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Case Report

Case Reports: Exploring the Varied Presentations and Clinical Features of Carney Complex, A Detailed Report on Three Distinct Cases

Altun İ et al. Different Faces of Carney Complex: Report of Three Cases

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What is already known on this topic?
• Already known fact 1 Carney Complex is characterized by multiple endocrine and nonendocrine manifestations.
• Already known fact 2 Variants in the PRKAR1A gene have been strongly associated with Carney Complex.

What this study adds?
• New information 1 These 3 cases represents three different PRKAR1A gene mutations, each associated with distinct clinical presentations. Our study highlight the absence of a consistent genotype-phenotype correlation in Carney Complex
• New information 2 Although PRKAR1A mutations are significantly associated with PPNAD, this report highlights that other adrenal pathologies may also contribute to the clinical spectrum of Carney Complex.

ABSTRACT
Carney Complex (CNC) is a rare genetic disorder characterized by multiple endocrine and nonendocrine neoplasms, primarily driven by mutations in the PRKAR1A gene. This study explores the clinical heterogeneity in CNC patients, with a focus on adrenal and extra adrenal involvement and its impact on patient outcomes. We present three pediatric cases with unique clinical manifestations. Case 1: A 12-year-old female with ACTH-independent cyclic Cushing syndrome due to primary pigmented nodular adrenocortical disease (PPNAD). The patient's condition progressed, leading to complications such as obesity, depression, and short stature, ultimately requiring bilateral adrenalectomy. Case 2: A 9-year-old male presented with an intranasal osteochondromyxoma and a large cell calcifying sertoli cell tumor. In the followup he developed hypocortisolism secondary to ACTH deficiency, with further complications including central precocious puberty and a growth hormone-secreting pituitary adenoma. Case 3: A 12-year-old female with adrenal insufficiency due to ACTH deficiency, complicated by a pituitary adenoma and a recurrent cardiac myxoma. Over time, the patient developed ACTH-independent Cushing syndrome secondary to PPNAD, necessitating bilateral adrenalectomy. Multiple fusiform aneurysms were also discovered after the recurrence of atrial myxoma. All cases highlight the absence of a consistent genotype-phenotype correlation in CNC, emphasizing the need for individualized management strategies. The findings underscore the complexity of diagnosing and treating CNC, particularly in pediatric populations, and call for further research into the underlying molecular mechanisms to develop more targeted therapies.
Keywords: ACTH-independent cyclic Cushing syndrome, Carney Syndrome, Case Report Primary Pigmented Nodular Adrenocortical Disease (PPNAD), PRKAR1A

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INTRODUCTION
Carney Complex (CNC) is a rare genetic disorder characterized by multiple endocrine neoplastic manifestations(1) . The majority of cases are autosomal dominant inheritance pattern with high penetrance but heterogeneous expression (1). In some instances, cases arise sporadically due to a de novo genetic defect (2). Inactivating mutations in the protein kinase A type I-alpha regulatory subunit(PRKAR1A) gene on chromosome 17q22-24 are found in most cases. Other gene mutations such as PDE11A, PRKACA, CTNNB1, PDE8B and ARMC5 are associated with CNC (3) .
The clinical manifestations of CNC vary widely and may include multiple endocrine neoplasms such as primary pigmented nodular adrenocortical disease (PPNAD), an adrenocorticotropin hormone (ACTH)-independent Cushing's syndrome, growth hormone (GH)-secreting and prolactin (PRL)-secreting pituitary adenomas, thyroid adenomas or carcinomas, testicular neoplasms like large-cell calcifying Sertoli cell tumours (LCCSCT) and ovarian lesions including cysts and cancinomas. Additionally, non-endocrine tumors such as cardiac myxomas, psammomatous melanotic schwannomas, breast myxomas, osteochondromyxomas (OMX) may also be observed(2,3) .
Due to genetic variability, CNC shows diverse phenotypes, requiring comprehensive evaluation with hormonal assays, imaging, genetic testing. Diagnosis is confirmed by meeting two major or one major plus one supplemental criterion (Table1) (4–6) .
The management of CNC requires a multidisciplinary approach due to the diverse clinical manifestations affecting multiple organ systems. (4,7) Pediatric patients often present with an earlier onset, more aggressive disease progression and distinct manifestations, making early diagnosis and personalized interventions critical for improving long-term outcomes (4,7). This study aims to highlight the clinical heterogeneity observed in pediatric CNC patients with PRKAR1A mutations, with a particular emphasis on the spectrum of adrenal involvement and its implications for patient outcomes. Written informed consent was obtained from the parents of all three patients for the use of their clinical data

CASE REPORTS

Case 1
A 5-year-old female patient presented to our clinic with intermittent episodes of unexplained edema, weight gain and the onset of pubarche in the absence of thelarche. During the physical examination in the symptomatic period, physical examination revealed Cushingoid features, including facial plethora and centripetal obesity with fat deposits primarily in the trunk and abdomen. Laboratory tests performed during

asymptomatic periods were normal; however, when symptoms recurred, the tests indicated hypercortisolism. Hormonal evaluations revealed significantly elevated serum cortisol levels, along with increased midnight plasma cortisol and elevated 24-hour urinary free cortisol excretion. Cortisol levels remained unsuppressed after low (1 mg) and high (2 mg 2 days) doses of dexamethasone supression tests (Table 2). The combination of elevated, non-suppressible cortisol levels and diffuse adrenal enlargement observed on MRI confirmed the diagnosis of ACTH-independent Cushing's syndrome which was cyclic regarding to it's intermitten course.

The patient's family history, including her mother's diagnosis of psammomatous melanotic schwannomas and breast ductal adenoma, along with the patient's clinical presentation, strongly suggested CNC. Genetic analysis confirmed this diagnosis by identifying a previously reported (8) heterozygous nonsense mutation in the PRKAR1A gene, c.289C>T(p.R297) (p.Arg97) (Figure 1). To rule out other CNC-associated comorbidities, comprehensive screening, including thyroid and pelvic ultrasonography, echocardiography, and brain-sellar MRI was performed, all of which revealed no abnormalities.

In the following she experienced 4-8 episodes of this clinical picture annually. By the age of 12, the frequency and severity of these episodes increased significantly, leading to severe central obesity(BMI: 28.7 kg/m2), short stature (height:-2.5 SDS), cortisol-induced insulin resistance, osteopenia and typical Cushingoid features and depressive symptoms. Progression of symptoms and their impacts on the patient's quality of life, lead to laparoscopic bilateral adrenalectomy by the age of 12. These histopathological findings are consistent with PPNAD, further supporting the clinical suspicion of CNC. Hydrocortisone and fludrocortisone replacement therapy was initiated postoperatively.

Case 2

The clinical characteristics of this patient up to the initial diagnosis of Carney Complex have been previously reported by Dagdeviren et al.(7) In brief, the male patient born to non-consanguineous healthy parents with an unremarkable perinatal history and no family history of tumors, first presented at six years of age with an intranasal mass that was surgically excised and initially diagnosed as fibrous dysplasia. During follow-up, he developed central precocious puberty requiring GnRH analogue therapy and scrotal ultrasonography revealed bilateral testicular macrocalcifications. At nine years of age, he presented with recurrent nasal obstruction and imaging demonstrated a calcified mass extending into the sphenoid sinus. At that point, the patient was referred to our clinic for endocrine evaluation. Endocrine evaluation showed ACTH deficiency associated with partial empty sella, necessitating hydrocortisone replacement. Despite repeated resections, the nasal lesion exhibited ambiguous histopathological and radiologic features. Biopsy of the macrocalcified testicular lesions confirmed LCCSCT, raising suspicion for Carney Complex and prompting reassessment of the nasal mass, which was subsequently reclassified as OMX. The combination of LCCSCT, OMX and cutaneous myxomas(Table 2) established the clinical diagnosis of Carney Complex, which was later genetically confirmed a previously reported(9) heterozygous nonsense mutation, c.672G>A (p.Trp224*) in the PRKAR1A gene (Figure 1). (7)

During the follow-up, at eleven years of age, he presented with excessive growth. His laboratory evaluation revealed elevated GH (3.82 ng/ml) and IGF1 (2.19 SDS) levels which were not suppressed below 1 µg/L after an oral glucose tolerance test (OGTT). At this point pituitary MRI was normal. At thirteen years of age, his growth accelerated more (weight: 0.71 SDS), height: 2.03 SDS, body mass index -0.24 SDS) which associated with increased GH (11.37 ng/ml) and IGF1(7.1 SDS) levels. GH levels not suppressed after an OGTT second times. Since no adenoma was identified on pituitary MRI at that stage, a conservative follow-up approach was adopted and treatment with a short-acting somatostatin analogue was initiated. After 2 months, short-acting somatostatin analog therapy was changed long acting somatostatin analog therapy monthly. Hyperprolactinemia and hypercortisolemia were not detected.

Despite maximum-dose somatostatin therapy, GH and IGF-1 levels remained elevated and growth acceleration persisted (height: +2.42 SDS). Pituitary MRI at this time revealed a 4mm pituitary adenoma. Transsphenoidal resection of the tumor was performed at the age of 16 years. However, post-surgery, GH and IGF-1 levels remained elevated, which required continous of long-acting somatostatin analog therapy.

Case 3

A 12-year-old female patient was referred to our clinic due to adrenal insufficiency diagnosed during the diagnostic workup for recurrent headaches. Her anthropometric measurements (weight: -0.6 SDS, height:+1.01 SDS, BMI:+1.5 SDS) were normal. Physical examination was unremarkable, except for the presence of spotty hyperpigmented skin lesions consistent with lentigines.

Laboratory evaluation showed a low serum cortisol level associated with a low serum ACTH level (Table 2). ACTH deficiency was confirmed by a low-dose ACTH stimulation test. Pituitary MRI revealed 3.5 mm pituitary adenoma. All other pituitary hormone concentrations were within normal limits. Hydrocortisone replacement therapy was initiated.

The patient was the first child of nonconsanguineous parents, with an unremarkable birth history. Her family history was significant for her mother's history of Cushing syndrome and central nervous system tumor.

Her medical history revealed that at the age of four, she presented to the pediatric emergency department with shortness of breath and pleuritic chest pain. Transthoracic echocardiography demonstrated a large intracardiac myxoma measuring 49 × 29 mm located in the right atrium. She subsequently underwent surgical resection of the myxoma.

Based on her clinical findings, medical and family history, CNC was suspected. Genetic analysis was performed, revealing a novel heterozygous mutation, c.249_250dup (p.Pro84LeufsTer46) in the PRKAR1A gene (Figure 1).

At 13.5 years of age, while receiving hydrocortisone therapy, the patient developed a cushingoid appearance. Despite discontinuation of hydrocortisone, clinical features of hypercortisolism persisted. She experienced progressive weight gain accompanied by impaired linear growth. Her anthropometric measurements at that time indicated a weight SDS of +1.81, height SDS of –1.08 and BMI SDS of +2.38. Physical examination revealed purple striae on the abdomen and acanthosis nigricans in the skin folds. Hormonal tests indicated elevated serum cortisol levels with low ACTH levels, disrupted diurnal rhythm, and increased 24-hour urinary free cortisol excretion. Cortisol levels remained unsuppressed after low (1 mg) and high (2 mg 2 days) doses of dexamethasone supression tests with elevated midnight plasma cortisol. Diffuse bilateral adrenal enlargement observed on MRI, a diagnosis of ACTH-independent Cushing's syndrome was established. The patient underwent bilateral total adrenalectomy via a traditional thoracoabdominal surgical approach. Histopathological examination confirmed the diagnosis of PPNAD. Postoperatively, hydrocortisone and fludrocortisone replacement therapy was initiated.

In the follow up patient developed central hypothyroidism secondary to the pituitary adenoma, and LT4 treatment was started six months later. At 15 years of age, routine echocardiography revealed a recurrent cardiac myxoma in the left atrium, necessitating repeat sternotomy and resection. Two months after myxoma resection, she presented with left arm and leg paresthesia and generelized seizure. Cranial MRI revealed multiple intraparenchymal cerebral hemorrhagic foci and cerebral digital subtraction angiography (DSA) demonstrated multiple fusiform aneurysms of several cerebral arteries. Endovascular embolization was performed for oncotic aneurysms located at the superior trunk frontal segment of the left middle cerebral artery (MCA) and at the distal cortical branch of the right posterior cerebral artery (PCA), along with their respective parent arteries.

DISCUSSION

This study presents three different patients with CNC with various PRKAR1A gene mutations, each with unique clinical manifestations and management challenges, thereby highlighting the complexity of the syndrome.

Indeed, as observed in our cases, CNC-related clinical features typically develop progressively over time (5). De novo mutations have been reported and the phenotype can vary significantly even among family members with the same genetic mutation. In our study, cases 1 and 3 had a family history of CNC, while case 2 was found to have a de novo mutation.

Adrenal Manifestations

One of the most common endocrine abnormalities in CNC is PPNAD, a rare form of ACTH-independent Cushing's syndrome(10). It is reported in the literature that PPNAD is observed in approximately 90% of CNC patients (2,9,11). Although PRKAR1A mutations are significantly associated with PPNAD, other adrenal pathologies also play a critical role in the clinical heterogeneity of CNC.
In the presented cases , various adrenal pathologies were identified. In Case 1, PPNAD was identified as the underlying cause of cyclic Cushing syndrome, consistent with existing literature. Conversely, in Case 2, adrenal insufficiency developed as a result of ACTH deficiency, which was attributed to empty sella syndrome. Although ACTH deficiency-related hypocortisolism has been documented in CNC, it remains a relatively rare manifestation of the syndrome (4). In Case 3, adrenal insufficiency initially presented due to a pituitary adenoma but subsequently progressed to ACTH-independent Cushing syndrome secondary to PPNAD. All baseline screening tests for hypercortisolism were performed sequentially because Case 3 had a known pituitary microadenoma, raising the possibility of pituitary-dependent Cushing disease in addition to PRKAR1A-related adrenal pathology. However, despite this suspicion, the biochemical findings were consistent with ACTH-independent hypercortisolism.Our approach to PPNAD management follows literature-based indications, with bilateral adrenalectomy as the standard treatment. Currently, there are no established protocols for the medical management of hypercortisolism in PPNAD, and data remain scarce; however, medical therapy with metyrapone has been attempted in a few reported cases(12)**.** These cases highlight the unpredictable nature of CNC's clinical course and the dynamic presentation of adrenal pathologies.

Extra-Adrenal Clinical Manifestations

Beyond adrenal pathology, our study identified a variety of additional clinical manifestations associated with CNC. Previous studies have demonstrated that CNC-related tumors frequently involve the heart, testicles, skin, thyroid, and central nervous system. Clinical work-up for all the manifestations of CNC should be performed at least once a year in all patients (2,4,9,13,14).

Cardiac

Among extra-adrenal tumors, cardiac myxomas represent one of the most life-threatening manifestations of CNC. These tumors tend to be multifocal, recurrent, and may arise at a younger age compared to sporadic cases (9,15,16).
In our study, Case 3 developed a recurrent cardiac myxoma, which was first identified during early childhood in right atrium and later required a repeat sternotomy for resection in the left atrium in adolescence. This is consistent with previous reports indicating that CNC-related cardiac myxomas exhibit recurrence (16) and should be removed surgically, warranting long-term echocardiographic monitoring even after successful surgical resection (16) .
Unlike sporadic myxomas, which predominantly affect the left atrium, CNC-associated myxomas can occur in all four cardiac chambers, often presenting with cardiac complications such as embolization, arrhythmias, or heart failure symptoms (13–18) .

Testis

The diagnosis of LCCSCT in the second case raised suspicion for Carney Complex, leading to a re-evaluation of the biopsy specimen, which revealed features consistent with osteochondromyxoma (OMX), a known component of Carney Complex. As noted in the literature (19) , LCCSCT is a common testicular tumor in CNC, typically benign but capable of causing hormonal activity (4). Annual testicular ultrasound screening is recommended for early detection, particularly in patients presenting with precocious puberty, testicular enlargement.

Pituitary and Cranial

Pituitary tumors, particularly GH-secreting adenomas, are well-recognized but less common features of CNC, occurring in approximately 10-12% of affected individuals (4). GH-secreting adenomas in CNC patients are typically diagnosed at an earlier age than in sporadic cases and may exhibit aggressive growth patterns with incomplete surgical remission (4) . This aligns with our findings in Case 2, in whom elevated GH and IGF-1 levels were detected biochemically before the adenoma became radiologically evident, leading to the initiation of medical therapy with a somatostatin analogue. After a GH-secreting pituitary adenoma was later identified on MRI, the patient underwent transsphenoidal resection due to inadequate biochemical control. However, GH levels remained elevated postoperatively, necessitating long-acting somatostatin analog therapy. Given the high recurrence rate and incomplete response to surgery, CNC patients with GH-secreting adenomas require lifelong IGF-1 monitoring, serial MRI evaluations, and necessiates adjunctive somatostatin analogs or dopamine agonists (20).
Case 3 developed central hypothyroidism secondary to a pituitary adenoma, requiring levothyroxine replacement therapy. While hypothyroidism is less frequently reported in CNC, its occurrence underscores the importance of regular thyroid function assessment, particularly in patients with concomitant pituitary involvement.
Case 3 presents multiple fusiform intracranial aneurysms. Their association with CNC may result from several mechanisms: a coincidental finding (though unlikely due to rarity), a delayed complication of cardiac myxoma caused by tumor emboli weakening vessel walls, or part of the Carney complex spectrum, similar to other connective tissue disorders(21–23).

Skin lesion

Cutaneous findings, especially spotty pigmentation (lentigines) and blue nevi, are early(2,10) and consistent features of CNC, often appearing on the face, lips, conjunctiva providing an important diagnostic clue(4)
Cases 2 and 3 exhibited characteristic lentigines, supporting their diagnosis of CNC. While these lesions are benign, their presence should prompt a thorough systemic evaluation, particularly in patients with a family history of CNC.

Thyroid

Although the presented cases did not show any evidence of primary thyroid disorder, thyroid abnormalities are increasingly recognized in CNC patients (24). Thyroid nodules in CNC may range from benign to thyroid carcinoma, emphasizing the need for routine thyroid function testing and ultrasound surveillance (24).

CONCLUSION

In conclusion, the diverse and unpredictable nature of CNC presents significant challenges in clinical management. The lack of a consistent correlation between genotype and phenotype necessitates an individualized approach in the clinical management of CNC(10). Furthermore, advancing our understanding of the molecular mechanisms underlying CNC(25) could lead to the development of targeted therapeutic strategies, thereby improving the management of the diverse endocrine pathologies associated with this condition.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

ETHICAL APPROVAL

Ethical approval is not required for this study in accordance with local or national guidelines.

INFORMED CONSENT

Informed consent was taken from the parents of patient for publication.

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AUTHOR CONTRIBUTIONS

Medical Practices: Ilayda Altun, Hande Turan, Olcay Evliyaoğlu, Concept: Ilayda Altun, Design: İlayda Altun, Hande Turan, Data Collection or Processing: Ilayda Altun, Hande Turan, Elvan Bayramoğlu, Aydilek Dagdeviren, Olcay Evliyaoğlu,Hasan Karakaş, Mert Uçar, Gökçe Velioğlu Haşlak, Dilek Bingöl Aydın Analysis or Interpretation: Ilayda Altun, Hande Turan, Olcay Evliyaoglu. Literature,Search: Ilayda Altun, Writing:Ilayda Altun,Hande Turan, Olcay Evliyaoglu

DATA AVAILABILITY

The datasets generated and analyzed during this studyare available from the corresponding author on reasonable request.

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Table 1: Diagnostic criteria and Supplemental criteria of Carney Complex
Diagnostic criteria:
Major criteria
1. Spotty skin pigmentation with a typical distribution (lips, conjunctiva and inner or outer canthi, and 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

Table2: A Comprehensive Overview of PRKAR1A Gene Variants in Carney Complex and Their Clinical and Laboratory Features

	Case 1	**Case 2**	**Case 3**	
Heterozygous mutation in the PRKAR1A gene	c.289C>T (p.R297) (p.Arg97) (previously reported)	c.672G>A (p.Trp224*) (previously reported)	c.249_250dup (p.Pro84Leufs1er46) (novel)	
Family history	Her mother's history of psammomatous melanotic schwannomas and breast ductal adenoma	Absent De novo mutation	Her mother's history of Cushing syndrome and CNS tumor.	
Consaquity	nonconsanguineous parents	nonconsanguineous parents	nonconsanguineous parents	
Adrenal patologies	ACTH-independent cyclic Cushing's syndrome Primary pigmented nodular adrenocortical disease (PPNAD)	Seconder adrenal insufficiency due to partial empty sella	Seconder adrenal insufficiency due to pituatry adenom	ACTH-independent Cushing's syndrome Primary pigmented nodular adrenocortical disease (PPNAD)
Basal serum cortisol level	34.71 mcgr/dl	8 mcgr/dl	8,6 mcgr/dl	16,56 mcgr/dl
Serum ACTH level	1 pg/ml	1 pg/ml	3 pg/ml	1,47 pg/ml
24-hour urinary free cortisol excretion	198 and 167 µg/day (>70 µg/m^2/day)			221 µg/day and 254 µg/day (>70 µg/m^2/day)
1 mg dexamethasone suppression test	16.41 µg/dL			12,57µg/dL
2-day 2 mg dexamethasone suppression test	29 mcgr/dl			28 mcgr/dl
Low dose ACTH stimulation test		13.4 µg/dL	8.45 µg/dL	
Spotty pigmented skin lesions consistent with lentigines.	absent	present	present	
Endocrine and non endocrine other patologies		İntranasal osteochondromyxoma (OMX)	Reccurent cardiac myxoma	
		Central precocious puberty	Pituitary adenoma.	
		Large cell calcifying Sertoli cell tumor (LCCSCT)	Central hypothyroidism	
		Growth hormone-secreting pituitary adenoma.		

Figure 1: PRKAR1A DNA analysis. Electropherogram showing the PRKAR1A variant found in the DNA extracted from the patient's blood. **A**, Case 1, **B.** Case 2, **C.** Case 3