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Case Report

A Case of Carney Complex with Pontine Glioma

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Gülümay Vural Topaktaş[1], Emrullah Arslan[1], Tayfun Çinleti [2], Özlem Anlaş[3], Ebru Pala[4], Benay Turan[1], Eren Er[1], Bumin Nuri Dündar[5]
[1]İzmir City Hospital Pediatric Endocrinology Clinic, İzmir, Türkiye
[2]İzmir City Hospital Pediatric Genetic Diseases Clinic, İzmir, Türkiye
[3]İzmir City Hospital Genetic Diseases Evaluation Center, İzmir, Türkiye
[4]İzmir City Hospital Department of Pathology, İzmir, Türkiye
[5]İzmir Katip Çelebi University Faculty of Medicine, Pediatric Endocrinology Division, İzmir, Türkiye

Abstract
Carney Complex (CNC) is a rare autosomal dominant syndrome characterized by skin pigmentation abnormalities, endocrine tumors, and cardiac myxomas. This report presents an 11-year-old girl with a history of pontine glioma treated with chemotherapy and radiotherapy at 2.5 years of age, who presented with complaints of weight gain and short stature, along with syndromic features (multiple nevi around the mouth and nose, four café-au-lait spots, and bilateral clinodactyly of the fourth toes) identified during physical examination. Genetic testing revealed a novel pathogenic *PRKAR1A* variant, confirming the diagnosis of CNC. The patient was diagnosed with Cushing's syndrome due to unsuppressed cortisol levels observed in a high-dose dexamethasone suppression test. Pathological evaluation following unilateral adrenalectomy confirmed the presence of primary pigmented nodular adrenocortical disease (PPNAD). This case highlights the importance of recognizing the atypical course of CNC to prevent delays in diagnosis and treatment.
Keywords: Carney complex, pontine glioma, Cushing's syndrome, short stature

Gülümay Vural Topaktaş, İzmir City Hospital Pediatric Endocrinology Clinic, İzmir, Türkiye
gulumayvural@hotmail.com
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Introduction
Carney Complex (CNC) is a rare autosomal dominant genetic disorder, first delineated by Carney et al. in 1985, characterized by cutaneous pigmentation abnormalities, cardiac and cutaneous myxomas, endocrine gland neoplasms or hyperfunction, and schwannomas (1, 2). Affected individuals may present with various endocrine manifestations, including primary pigmented nodular adrenocortical disease (PPNAD), growth hormone-secreting pituitary adenomas, prolactinomas, thyroid adenomas or carcinomas, and gonadal tumors, with two or more endocrine tumors often observed.(3) The clinical presentation of CNC varies widely, ranging from multiple concurrent features to a single isolated manifestation. The components of CNC can manifest at any age, which may complicate the diagnosis in certain cases. PPNAD is a rare cause of ACTH-independent Cushing's syndrome(CS). ACTH-independent CS due to PPNAD has been found to be associated with CNC in 90% of cases(4).It represents the most common endocrine hyperactivity in CNC and occurs in approximately 25% of affected individuals. However, the incidence may be underestimated due to atypical and subclinical disease presentations. In autopsy studies conducted on patients with CNC, PPNAD was observed in nearly all cases.(3-5)
In this article, we present a case of a patient with a history of pontine glioma who presented with short stature and obesity. Comprehensive evaluations led to a genetic diagnosis of CNC, followed by the identification of CS.

Case Report
An 11-year-old female patient presented with significant weight gain over the past six months and short stature noted over the preceding 1–2 years. Her medical history reveals a diagnosis of pontine glioma at the age of 2.5 years, identified during the evaluation of neurological symptoms, for which she underwent chemotherapy with temozolomide and radiotherapy at a total dose of 54 Gy. There was no consanguinity between the mother and the father. No history of pathological short stature or genetic disorders was reported in the family history. Physical examination revealed a body weight of 48 kg (+0.98 SDS), a height of 136 cm (-1.6 SDS), a BMI of 25.95 (+2.06 SDS). Her pubertal development was compatible with Tanner stage 5. The patient, who had a reported age of menarche at 9,5 years, exhibited regular menstruation.Clinical findings included proportional short stature, central obesity, multiple nevi around the mouth and nose, four café-au-lait spots(The largest café-au-lait spot (2.5×1.5 cm) was located in the interscapular region. Additionally, two smaller café-au-lait spots (<1×1 cm) were present on the posterior aspect of the right upper leg, and one spot (<1×1 cm) was located at the sacral level), and bilateral clinodactyly of the fourth toes (Figure 1). Considering the patient's early menarche (potentially indicative of precocious puberty or rapidly progressing puberty), short stature, history of an intracranial mass, obesity, skin lesions, and syndromic features, further investigations were initiated with the preliminary consideration of a disorder from the Rasopathy group.
Biochemical tests conducted for the evaluation of short stature were within normal limits, and celiac tests were negative. The patient's IGF-1 level was found to be low (72.1 ng/mL, -2.35 SDS), and bone age was consistent with 15 years (Table 1). Anterior pituitary hormone levels, assessed due to prior radiotherapy to the head and neck region and were evaluated as appropriate for her age and pubertal stage.
Genetic analysis, including a broad-spectrum panel, was performed due to the patient's clinical features. While CNC is not classified as a Rasopathy, this panel was utilized due to overlapping clinical features. The genetic panel analysis identified a novel heterozygous pathogenic variant, c.51dup (p.Cys18MetfsTer2), in the PRKAR1A gene (ENST00000589228), which is associated with autosomal dominant CNC type 1.
The variant has a reported maximum population frequency of 0.0% in the gnomAD genome database.
The ENST00000589228(*PRKAR1A):* c.51dup (p. Cys18MetfsTer2) variant, caused by a single-base insertion, leads to a frameshift mutation and loss of function of the *PRKAR1A* protein. According to the American College of Medical Genetics and Genomics (ACMG) criteria and segregation analysis, this novel variant is classified as 'pathogenic' based on PVS1, PM2, and PP1 scores. Segregation analysis confirmed the presence of this variant in the affected father, while it was absent in the mother. A detailed physical examination of the father revealed hyperpigmented macules on the lips as the sole clinical manifestation, with no additional abnormalities detected. The father was subsequently referred to adult endocrinology for comprehensive evaluation and further diagnostic screening. Subsequent to the genetic analysis, further communication with the family disclosed the presence of a previously unacknowledged paternal uncle who had undergone bilateral adrenalectomy and remained under ongoing medical surveillance for a confirmed diagnosis of PPNAD.

The patient underwent comprehensive screening for other components of CNC. Echocardiography did not reveal any evidence of cardiac myxomas, and in thyroid and pelvic ultrasonography there were no pathological finding. Due to the patient's history of short stature and obesity, along with the well-established association between CNC, PPNAD, and ACTH-independent CS, further evaluation was conducted. Circadian cortisol rhythm analysis showed unsuppressed nighttime serum cortisol levels, consistent with an impaired diurnal rhythm (5.29 µg/dL). Suppression tests, including overnight dexamethasone suppression and low-dose dexamethasone suppression, showed unsuppressed cortisol levels (4.02 µg/dL and 4.66 µg/dL, respectively). Urinary free cortisol levels were mildly elevated (16.6 µg/24 h; normal <37 µg/24 h). A high-dose Liddle test revealed a paradoxical increase in urinary free cortisol levels (Table 2).

Dynamic contrast-enhanced computed tomography of the adrenal glands demonstrated a 6×5 mm lobulated lesion in the body of the left adrenal gland and a millimetric calcified focus in the medial limb of the right adrenal gland. The patient underwent unilateral adrenalectomy of the left adrenal gland. Histopathological examination revealed multiple pigmented micronodules in the adrenal cortex, all smaller than 1 cm (most <1 mm), consistent with PPNAD **(Figures 2 and 3).**

No complications were observed after the operation and the patient remains under regular follow-up. Four months after unilateral adrenalectomy, the serum cortisol levels were measured as 10.3 µg/dL at 08:00 AM and 2.35 µg/dL at 11:00 PM. The 24-hour urinary free cortisol level was 10.1 µg/24 hours (N: <34). At present, our patient has no additional complaints; however, ongoing follow-up is being conducted to monitor existing findings, evaluate the response to treatment, and identify the emergence of new manifestations. For endocrine complications of CNC, annual measurement of urinary free cortisol levels is planned for PPNAD monitoring. In cases of clinical suspicion, diurnal cortisol levels (with samples taken at 11:30 PM, 12:00 AM, 7:30 AM, and 8:00 AM), a dexamethasone suppression test (modified Liddle's test), and an adrenal CT examination will be conducted. For thyroid tumors, an annual thyroid ultrasound is recommended. If there is clinical suspicion for ovarian tumors, a suprapubic ultrasound will be performed. In cases of suspected gigantism and/or acromegaly, pituitary MRI will be performed to evaluate for pituitary adenomas. Additionally, a 3-hour oral glucose tolerance test (OGTT) and a 90-minute thyrotropin-releasing hormone (TRH) stimulation test will be conducted when necessary.

(Parental consent was obtained and is attached under the title "Parental Consent.")

Discussion

Our case, who was referred to our clinic due to short stature and obesity and diagnosed with CNC, is an interesting case due to the atypical features of CNC. Our case is the first in the literature to describe the coexistence of pontine glioma and CNC. Additionally, it is important to note that in our case with precocious puberty and a history of cranial RT, the CS findings may be overlooked due to their subtlety, which could explain the short stature. The father's very mild CNC findings, despite carrying the same variant, also highlight the difference in expression. As in our case, we believe that even in atypical presentations such as short stature, it is beneficial to keep CNC in mind and at least investigate the additional findings of CNC.CNC is classified as a multiple neoplasia syndrome with an autosomal dominant inheritance pattern(1). Patients may present with the characteristic clinical features of CNC, but, as demonstrated in this case, the condition can also be identified in pediatric patients presenting to endocrinology clinics with nonspecific complaints such as short stature. The clinical manifestations of CNC are highly variable, even among members of the same family(3).

Approximately 50% of CNC families reported in the literature have mutations in the *PRKAR1A* gene located on chromosome 17q22-24. The *PRKAR1A* gene, identified in this case in the patient and her father, encodes the regulatory subunit type 1α (R1α) of protein kinase A (PKA), a classical tumor suppressor protein. PKA is integral to numerous endocrine signaling pathways. The R1α subunit inhibits PKA activity, and mutations in *PRKAR1A* result in the production of a truncated, nonfunctional protein. This leads to increased PKA activity, resulting in intracellular signaling dysregulation and, subsequently, endocrine hyperfunction or tumorigenesis(3, 6, 7).

Currently, approximately 62% of CNC cases have identifiable pathogenic *PRKAR1A* variants, with about 70% of these cases attributed to mutations in *PRKAR1A* (60% detected through sequencing and 10% via deletion-duplication analysis). In the remaining 30% of cases, the genetic basis remains unknown. Bertherat et al., in the largest study to date, identified *PRKAR1A* mutations in 114 of 185 CNC families (62%), underscoring the critical role of this gene in CNC pathogenesis(8).

Although universal diagnostic criteria for Carney Complex (CNC) have not yet been established, a revision has been reported in 2001 that introduced major and minor diagnostic criteria, enhancing diagnostic sensitivity to approximately 98%(3). In this case, a comprehensive clinical evaluation and thorough patient history satisfied the diagnostic criteria even prior to the confirmation of the diagnosis through genetic testing.

The association between CNC and CS has been well-documented. A study by Cazabat et al. demonstrated that among CNC patients presenting with CS secondary to PPNAD, the frequency of identifying pathogenic *PRKAR1A* variants increased to 80%(9). CS is a significant and potentially life-threatening component of CNC. While CS can present with overt clinical symptoms, it may also manifest in an atypical manner, as observed in this case, where only mild Cushingoid features were present alongside disrupted diurnal cortisol rhythms. Diagnostic confirmation can be achieved using high-dose dexamethasone suppression testing, which reveals cortisol non-suppression, or by identifying paradoxical increases in 24-hour urinary free cortisol levels.

A retrospective analysis conducted at the Mayo Clinic identified 37 patients with CNC. These patients were classified into four categories: classical CS (consistent clinical and laboratory findings), subclinical CS (absence of clinical symptoms but laboratory findings consistent with CS), possible CS (presence of some clinical findings with borderline results in one or more tests defining classical CS or adrenal pathological findings), and no CS (absence of both clinical and laboratory findings indicative of CS). Among the 17 patients diagnosed with classical CS, 15 underwent surgical intervention, including bilateral adrenalectomy (9 patients), subtotal adrenalectomy (2 patients), and partial unilateral adrenalectomy (4 patients), while 2 cases were diagnosed through autopsy reports. All patients who underwent bilateral adrenalectomy achieved complete remission. In the subtotaladrenalectomy group, remission was achieved in both patients, although one developed adrenal insufficiency. In the partial unilateral adrenalectomy group, two patients experienced recurrence of CS during follow-up and subsequently underwent total adrenalectomy.For the 12 patients with subclinical or possible CS, long-term follow-up without intervention, ranging from 1 to 36 years (mean: 10 years), demonstrated no progression to overt CS. Similarly, among the 8 patients classified as having no CS, follow-up over 2 to 49 years (mean: 19.5 years) revealed no evidence of CS development.Notably, one patient remained untreated for nearly 30 years, while another exhibited spontaneous remission of CS. Furthermore, PPNAD was identified in two patients who exhibited no clinical features of CS, emphasizing the potential for subclinical adrenal involvement in CNC(10). Cushing syndrome due to PPNAD must be treated to manage the consequences of cortisol overproduction. In rare cases, anti-cortisol medical treatments such as ketoconazole or mitotane have been used; however, surgical options still remain the primary approach today(11, 12)

Although bilateral adrenalectomy remains the standard treatment for PPNAD, literature reports indicate heterogeneous clinical responses following unilateral adrenalectomy, with rare cases demonstrating sustained remission of Cushing syndrome (CS) for up to nine years postoperatively (10, 13-15). These findings suggest the need to reconsider performing partial rather than total bilateral adrenalectomy in patients with CNC and CS.

In the present case, considering the patient's young age, the unilateral nature of the adrenal lesion, and existing evidence suggesting relatively prolonged remission periods following unilateral adrenalectomy in select cases, a comprehensive evaluation of potential clinical outcomes was conducted in consultation with the patient's family. Following a multidisciplinary consensus with the surgical team, unilateral adrenalectomy was deemed the most appropriate therapeutic approach. In our patient who underwent unilateral adrenalectomy, the most recent evaluation showed regression of CS findings, with no evidence of adrenal insufficiency.

Upon reviewing the existing literature, no documented association between CNC and pontine glioma has been identified. In our case, the pontine glioma has been considered a different presentation of CNC. Further research is needed to elucidate the potential relationship between CNC and intracranial masses, including pontine gliomas.

Previous studies have highlighted that CNC can exhibit clinical variability even among members of the same family and that the diagnostic process may be delayed for years. To expedite diagnosis, increasing awareness of the disease's multifaceted manifestations, obtaining a detailed medical history of patients and their families, and being vigilant about diagnostic pitfalls are essential. Notably, the presence of unusual symptom combinations should prompt clinicians to consider rare endocrinopathy syndromes such as CNC (16).This case emphasizes the importance of recognizing CNC as a rare but critical condition with systemic and endocrine manifestations. Early diagnosis, comprehensive screening for associated features, and appropriate management strategies are essential to mitigate potential complications and improve patient outcomes.

Conclusion

CNC represents a rare etiology of endocrine tumors. Although the majority of CNC cases develop CS at some stage, its atypical clinical course frequently results in delayed diagnosis. In patients presenting with ACTH-independent CS, PPNAD should be considered as a potential underlying cause. Given that CNC and its associated complications can manifest at any point during the patient's lifetime, comprehensive screening for PPNAD is essential in all cases. Furthermore, genetic testing and surveillance should be extended to family members of affected individuals to facilitate early detection and mitigate the risk of life-threatening complications.

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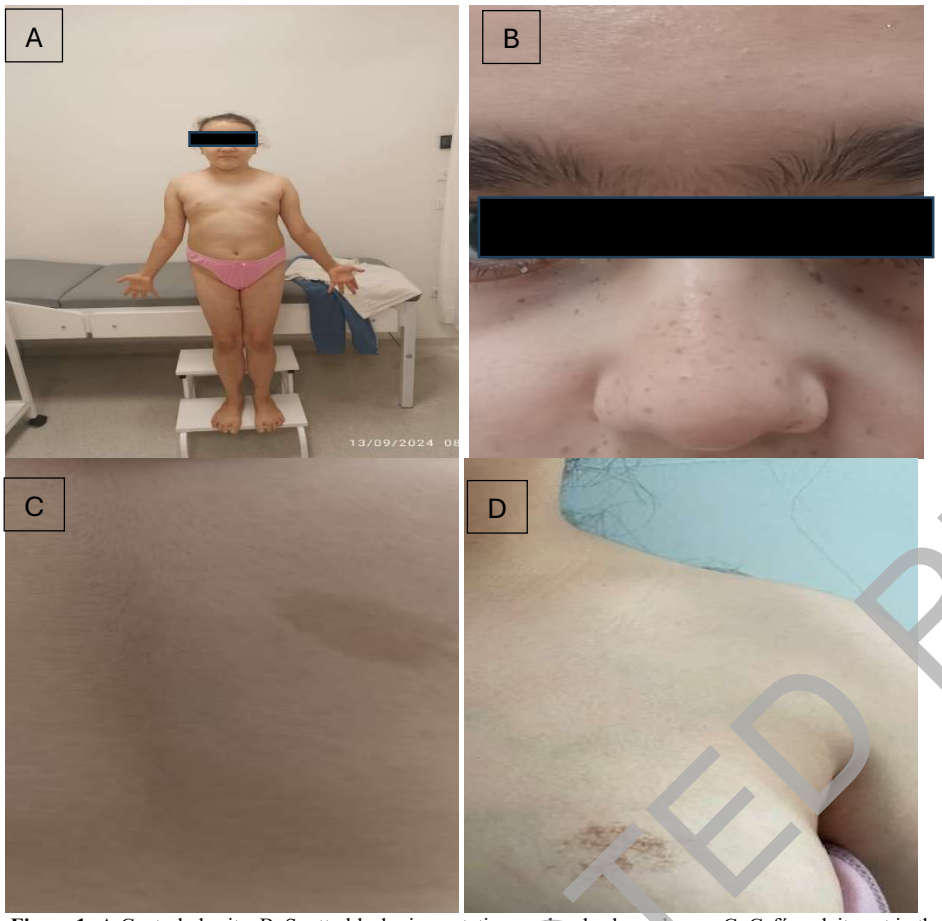

Figure 1: A:Central obesity, B: Spotty black pigmentation on the cheeks and nose, C: Café au-lait spot in the interscapular region, D: Lentiginous skin lesion on the upper left breast

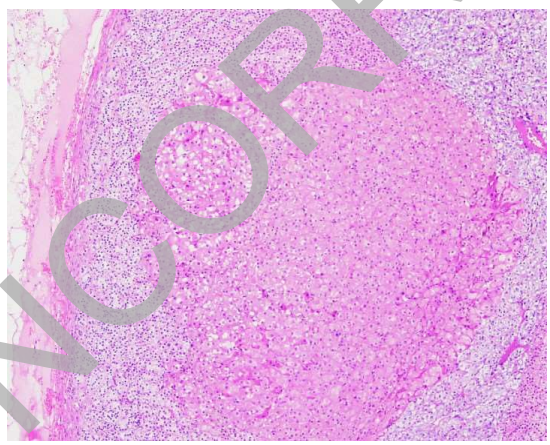

Figure 2: A micronodule (<1 cm) in the adrenal cortex, well-defined and composed of cells with eosinophilic cytoplasm (H&E stain, X100)))magnification)

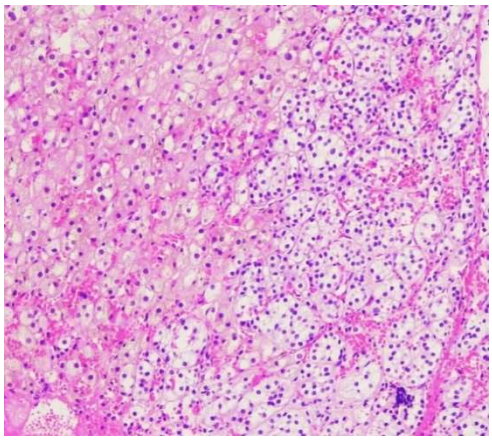

Figure 3: Cytoplasmic lipofuscin pigment in adrenal cortical micronodules (H&E stain, X200 magnification)

GLUCOSE	82 mg/dl (N:70-110)	**TSH (Thyroid-Stimulating Hormone)**	2.56 mU/L (N:0.51-4.30)
BUN (Blood Urea Nıtrogen)	8 mg/dl (N:5-18)	**sT4 (Free Thyroxine)**	1.3 ng/dl (N:0.93-1.7)
CREATININE	0.41 mg/dl (N:0.39-0.73)	**FSH (Follicle-Stimulating Hormone)**	4.41 U/L (N: 0.4-8.6)
SODIUM	140 mmol/L (N:136-145)	**LH (Luteinizing Hormone)**	3.51 U/L (N: 0.9-13.3)
POTASSIUM	4,8 mmol/L (N:3.5-5.1)	**Estradiol**	53.6 ng/L
LDL(Low-Densıty Lıpoproteın)	42 mg/dl (N:0-130)	**ACTH(Adrenocorticotropic Hormone)**	19.9 pg/ml
HDL(Hıgh-Densıty Lıpoproteın)	42 mg/dl (N:35-55)	**CORTISOL**	13.2 µg/dL
TOTAL CHOLESTEROL	173 mg/dl (N,92-200)	**IGF-1 (Insulin-Like Growth Factor-1)**	**72.1 ng/mL (-2.35 SDS)**
TRIGLYCERIDE	54 mg/dl (N:0-150)	**PROLACTIN**	8 µg/L (N:4.79-23.3)
URINE	Density: **1019** pH: **5**	**INSULIN**	6.83 mU/L

Table 1: The patient's initial diagnostic tests performed due to obesity and short stature

	LOW DOSE DEXAMETHASONE SUPRESSION TEST		**HIGH DOSE(LIDDLE) DEXAMETHASONE TEST**		
	BASAL	**FINAL**	**BASAL**	**DAY 1**	**FINAL**
Plasma cortısol(µg/dl)	13.2	**4.66**	15.5	13.4	**6.47**
Free cortısol İn urine (µg/24 h)	8.56	6.66	17.8	14.5	**26.6**

Table 2: Results of the suppression tests
(µg/dl: microgram /decilitre)
(µg/24 h: microgram/24 hour)

Evaluation of Low-Dose Dexamethasone Suppression Test Results

- If plasma cortisol is below 5 µg/dL and urinary free cortisol is below 10 µg/day, the result is considered normal.
- Alternatively, urinary free cortisol should be suppressed by more than 50%.

Evaluation of High-Dose (Liddle) Dexamethasone Test Results

- Urinary free cortisol may decrease by approximately 90% of the baseline value.
- Serum cortisol measured the morning after the last dose is suppressed by more than 90% of the baseline value.