Case Report

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# Unilateral Primary Pigmented Nodular Adrenocortical Disease: Report of a Rare Case

## Unilateral Primer Pigmente Nodüler Adrenokortikal Hastalık: Nadir Bir Olgu Sunumu

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**Abstract**

Primary pigmented adrenocortical disease is a rare disorder usually affecting both adrenals. It causes Cushing's syndrome that is adrenocorticotropic hormone independent. It is treated by bilateral adrenalectomy. We present an unusual case where this condition was unilateral and was diagnosed as adenoma on imaging. The patient was subsequently treated by unilateral adrenalectomy, and had no signs of recurrence in 5-year postoperative follow-up. This case emphasizes the importance of histopathology and immunohistochemistry in diagnosis of this condition.

**Keywords:** Primary pigmented adrenocortical disease, Cushing's syndrome, carney's complex

**Öz**

Primer pigmente nodüler adrenokortikal hastalık nadir bir hastalıktır ve genellikle her iki adrenali birlikte etkiler. Adrenokortikotropik hormon bağımsız Cushing sendromuna neden olur. Tedavisi bilateral adrenalektomidir. Biz burada bu hastalığın tek taraflı olduğu ve önceden görüntülemede adenom olarak bildirildiği ve ardından unilateral adrenalektomi uygulanan bir olguyu sunmaktayız. Hastanın postoperatif beş yıllık takibinde semptomlarda tekrarlama olmadı. Bu olgu bu hastalığın teşhisinde histopatoloji ve immünhistokimyanın önemini göstermektedir.

**Anahtar kelimeler:** Primer pigmente nodüler adrenokortikal hastalık, Cushing sendromu, carney kompleksi

### Introduction

Primary pigmented nodular adrenocortical disease (PPNAD) is a rare type of adrenal hyperplasia which may manifest as adrenocorticotropic hormone (ACTH)-independent Cushing's syndrome (CS). PPNAD is characterized by dark, pigmented micronodules (<10 mm) in the adrenal cortex. Fifty percent of cases of PPNAD are part of Carney complex (CNC), a multiple neoplasia syndrome, and the rest are sporadic cases (1). PPNAD may manifest with typical signs of CS, subclinical CS, atypical CS or cyclic CS. In the literature, bilateral adrenal involvement has been reported in most of the cases of PPNAD. Unilateral involvement is very unusual. The treatment of choice for PPNAD is bilateral adrenalectomy. We present a case of PPNAD in a 16-year-old male who presented with ACTH-independent CS and was diagnosed with adenoma of the left adrenal gland on clinical and radiologic grounds. The diagnosis of PPNAD was confirmed by histopathological and immunohistochemical studies, biochemical markers, and follow-up after laparoscopic adrenalectomy.

### Case Report

A 16-year-old male presented with central obesity, short stature, moon face, hump back, abdominal striae, and hypertension. The patient was on antihypertensive treatment for the past two years. His height was 125 cm and he weighed 65 kg (Figure 1a). His blood pressure was 160/100 mmHg. He was found to have a 24-hour urinary cortisol level of above 1000 mcg (biological reference interval: 28.5-213.7 mcg/24 hours). His ACTH levels were undetectable. Abdominal computed tomography (CT) showed a localized lesion in the left adrenal gland measuring 15x17 mm in size (Figure 1b). The right adrenal was found to be normal. CT images suggested a diagnosis of Cushing's syndrome associated with adrenal adenoma. Routine hematological and biochemical investigations were found to be within normal limits. The patient was taken for laparoscopic adrenalectomy. He was given a right lateral position, four ports were inserted and pneumoperitoneum was created. The colon was mobilized along the white line. Retroperitoneal fat was dissected from Gerota's fascia and the left adrenal was identified. The left adrenal gland was dissected free and excised. The specimen was removed and the port sites

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were closed. The left adrenal gland was sent for histopathologic investigation.

The gland measured approximately 5 cmx2.5 cmx2 cm in size and weighed 18 gm. It showed a rounded enlargement at one end making it tadpole-shaped. On cutting, a dark brown-black colored round mass of size 1.3x1.0 cm was seen (macronodule) along with tiny dark nodules in the rest of the adrenal parenchyma (micronodules) (Figure 2a). On microscopy, the nodules consisted of large polygonal cells with abundant eosinophilic cytoplasm containing a brown granular pigment and having large nuclei with prominent nucleoli. The nodules were not capsulated. The intervening cortex showed atrophy (Figure 2b). There were focal dense collections of lymphocytes. Immunohistochemical staining using chromogranin (CMG, DAKO) and synaptophysin (SYN, DAKO clone SY38) was done. The cells forming nodules showed immunoreactivity to both stains and they were clearly separated from the surrounding cortex in the SYN stain because the surrounding cortex was negative for SYN (Figure 2c). The diagnosis of PPNAD was suggested. The patient was evaluated for the possibility of CNC using CT and thoracic and cranial magnetic resonance imaging and cardiological investigation, including echocardiogram was performed. Ultrasonography of the genitals was done. He did not have any contributory family history. The post-operative recovery of the patient was uneventful. At the time of hospital discharge, his blood pressure was 120/80 mmHg and he did not need any antihypertensive. His abdominal CT was reviewed and it was found that the right adrenal gland was within the normal limits. During his follow-up visit after six months, it was observed that his weight had decreased from 65 kg to 55 kg, his face was leaner, the hump on the back had disappeared, and his abdominal girth had reduced by 12 cm (Figure 3). His blood pressure was 120/80 mmHg. His 24-hour urinary cortisol level was within normal limits. An abdominal CT at this time showed a normal right adrenal. He refused adrenalectomy because of symptomatic improvement.

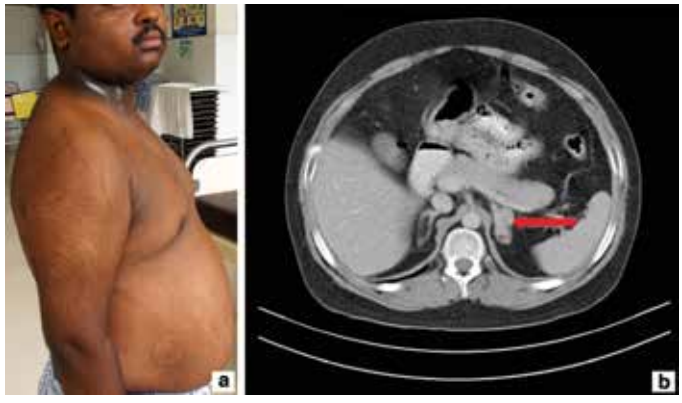


**Figure 1.** a) Preoperative clinical photograph showing central obesity, hump back and abdominal striae. b) Preoperative abdominal computed tomography scan showing the nodular lesion in left adrenal (red arrow)

## Discussion

PPNAD was first described by Chute in 1949 (2). It was named by Shenoy et al. (2) in 1984. It is a rare cause of ACTH-independent CS (1). It has a bimodal age incidence, most cases diagnosed in second and third decade, but a significant proportion of patients present during early childhood (3). Our case presented in the second decade. PPNAD affects both adrenal glands and is characterized by tiny brown-black micronodules (<10 mm) in the adrenal cortex. The adrenal glands may be normal in size (1). The nodules are dark and pigmented. On CT, the adrenal glands may appear as normal sized or large with bilateral nodularity. Microscopically, they consist of large cortical cells with eosinophilic cytoplasm and large hyperchromatic nuclei with prominent nucleoli. The cytoplasm contains lipofuchsin, a brown granular pigment. The intervening cortex is atrophic. The nodules are non-encapsulated. The nodules are positive for CMG and SYN (4). Immunohistochemistry for SYN clearly distinguishes PPNAD nodules from surrounding adrenocortical tissue and can be helpful in detection of small nodules in apparently unaffected cortex (4). Sometimes the nodules of PPNAD may be large in size. The largest reported macronodule was 3.5 cm in size (2).

PPNAD may be sporadic or familial. Many of the familial cases are a manifestation of CNC. Genetic studies indicate common molecular pathways involved in the pathogenesis of sporadic PPNAD or as a manifestation of CNC (3). CNC is a multiple neoplasia syndrome described in 1985 by Carney et al. (5). It is an autosomal dominant syndrome. Patients may have various associated conditions including, cardiac and cutaneous myxomas, breast myxomatosis, spotty skin pigmentation, pituitary adenomas with acromegaly, large-cell calcifying Sertoli cell tumors, adrenocortical lesions, Leydig cell tumors, psammomatous melanotic schwannoma,

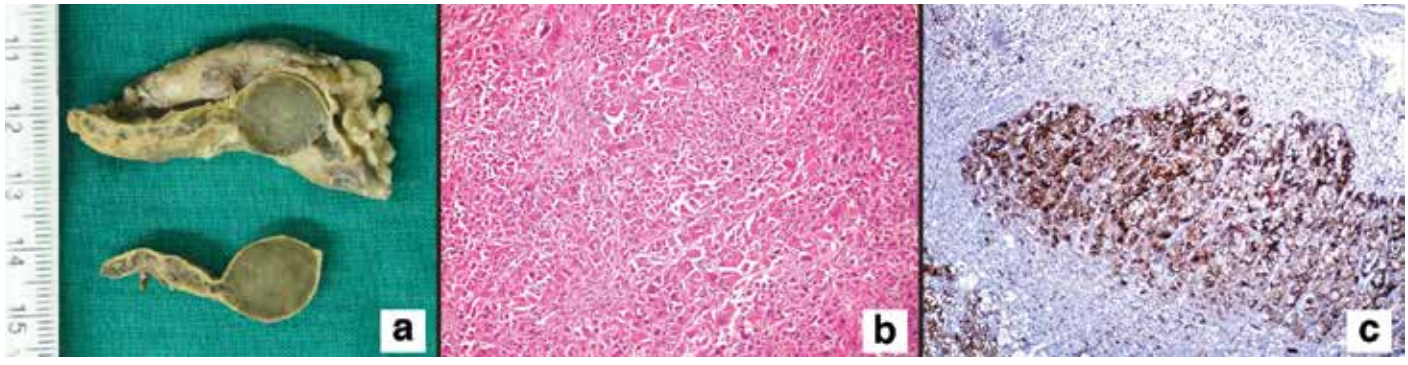


**Figure 2.** a) Gross specimen showing the tadpole shaped left adrenal gland with the macronodule as well as micronodules which are darkly pigmented. b) Histopathologic picture showing the nodules consisting of large polygonal cells with abundant eosinophilic cytoplasm, having large nuclei with prominent nucleoli (Haematoxylene and eosin x400). c) Immunohistochemistry showing the immunoreactivity of the nodules for synaptophysin (x100)

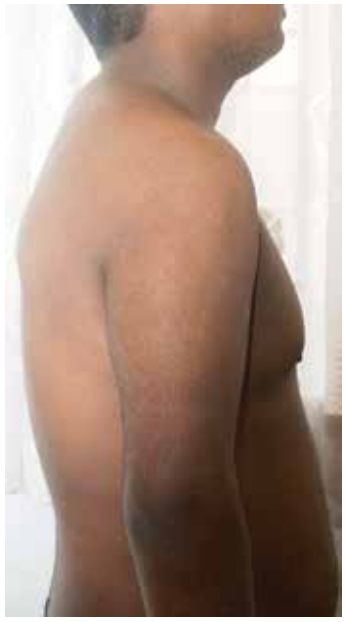

**Figure 3.** Clinical photograph, 6 mths postoperative showing the disappearance of central obesity and the hump back

epitheloid blue nevus, ductal adenoma of the breast, and thyroid follicular neoplasms both benign and malignant. Clinical picture of CNC may vary from patient to patient even among members of the same family (6). A tumour suppressor gene on long arm of chromosome 17 (17q22-24), PRKAR1A is found to be mutated in about half the families with CNC (3,5). This leads to formation of various tumors (6). Mutations of chromosome 2 p16 locus are also found in families of CNC. Genetic testing was not done in our case. Clinically, patients with PPNAD may present with classical CS as in our case. They sometimes present with an atypical form of CS, where the patient is thin instead of obese (3). This is due to severe osteoporosis, short stature and severe muscle and skin wasting (3). These patients may have a normal 24-hour urinary cortisol, but characteristically show absence of circadian rhythm (3). Occasionally, periodic CS is found where days or weeks of hypercortisolism alternate with similar periods of normal levels (1,3). Periodic CS is more often seen in children and adolescents (3). Patients with PPNAD typically show a paradoxical increase in urinary cortisol and/or 17-hydroxy-corticosteroids during the second phase of the Liddle's test (1,3) (Liddle's test is done in two phases; low dose and high dose. Two days of baseline urinary cortisol levels followed by two days of 0.5 mg dexamethasone given every six hours per os. This is followed by two days of 2 mg dexamethasone given every six hours per os and urinary cortisol levels are measured on the sixth day of the test). More than 50% increase in relation to baseline value identifies approximately 70% of PPNAD cases, and is a major criteria for diagnosis of CNC (6). A 100% increase in relation to baseline identifies PPNAD cases alone (6). This delayed paradoxical response is associated with increased expression of glucocorticoid receptors in the adrenal cortical cells (1). In the present case, the diagnosis of CS was based on typical clinical features with markedly high urinary cortisol levels and, PPNAD was confirmed as the cause after histopathological investigation. Since the radiological evaluation indicated adenoma of the adrenal gland a Liddle's test was not ordered. Postoperatively, the blood pressure returned to normal and at 6 month follow-up, relief of symptoms and normal urinary cortisol levels were observed. The patient is normotensive without antihypertensives up to the time of writing of this manuscript.

## Conclusion

PPNAD is a rare cause of ACTH-independent CS. Various modalities used in the diagnosis of PPNAD include CT, histopathology and the Liddle's test. Adrenal imaging alone can be misleading as in our case when macronodules are present. Features of CNC, when PPNAD is a manifestation of CNC, can help to lead to a correct diagnosis. Treatment of choice is bilateral adrenalectomy. There is a report of remission of hypercortisolism after unilateral adrenalectomy (7). When laboratory investigations indicate CS caused by adrenocortical tumor, but no obvious space occupying lesion is found by adrenal imaging, the possibility of PPNAD should be considered (8).

## *Authorship Contributions*

*Informed Consent: Consent form was filled out by all participants, Concept: Shreepad Bhat, Design: Snehal Purandare, Sanjay Deshmukh, Data Collection or Processing: Vandana Gaopande, Analysis or Interpretation: Vandana Gaopande, Literature Search: Vandana Gaopande, Writing: Vandana Gaopande, Peer-rewev: Internal peer-reviewed, Conflict of Interest: No conflict of interest was declared by the authors, Financial Disclosure: The authors declared that this study has received no financial support.*

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