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Cushing Syndrome Due to Pigmented Nodular Adrenal Hyperplasia in an Iranian Patient: A Case Report and Review of the Literature

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Abstract Primary pigmented nodular adrenocortical disease (PPNAD) is a rare cause of Adrenocorticotropic hormone-independent Cushing syndrome. In this case, we present a case of PPNAD in 25 y/o women who presented with a 3 years history of weight gain, hirsutism, and abnormal menstruation. Our findings were suggestive of PPNAD in the pathological study of adrenal biopsy.

Keywords: *Cushing syndrome, PPNAD, Primary pigmented nodular adrenocortical, hirsutism, low dose dexamethasone suppression test*

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1. Introduction

The diagnosis and treatment of Cushing's syndrome is sometimes challenging. The endogenous Cushing's syndrome includes adrenocorticotropic hormone (ACTH)-dependent (about 80%) and ACTH-independent (about 20%). Primary Pigmented Nodular Adrenocortical disease (PPNAD) is a rare cause of ACTH-independent Cushing's syndrome. PPNAD occurs sporadically or accompanies with the Carney complex (CNC) [1]. CNC was first described in 1985 by J Aidan Carney and co-workers at the Mayo Clinic [2]. PPNAD is the most common endocrine manifestation of CNC occurring in about 60% of affected patients [3]. However, the process of symptoms' development are sometimes slow, which makes the diagnosis difficult and time consuming [4,5]. In addition, some PPNAD cases have had a cyclic or episodic form of Cushing syndrome [6]. Therefore, determining the onset and duration of symptoms of hypercortisolism is not always feasible. Here, we present a woman who was referred for obesity, hirsutism and menstruation irregularities management, and finally was diagnosed with PPNAD.

2. Case Presentation

A 25-year-old Iranian woman came with history of obesity, hirsutism and menstruation irregularities since three years ago. She had received Metformin (500mg/TDS) and spironolactone (50mg/BD) as treatment. Her symptoms improved relatively, but she was still complaining of weight gain, hirsutism, alopecia, and irregular menstruation. Then she developed hypertension and proximal muscle weakness and primary care physician referred her to endocrinologist for further assessment and ruling out Cushing's syndrome.

She had normal values of laboratory tests including complete metabolic panel and thyroid hormones. 24-hour urinary cortisol concentration was high (551 µg/24hours with normal range: 30-137). Her basal plasma cortisol level was 23 µg /dl at 8 am and basal ACTH level was low (1 pg/ml). Serum level of cortisol after overnight dexamethasone suppression test and low-dose dexamethasone suppression test (LDDST) were high (27.5 and 28.9 µg/dl respectively). Serum level of dehydroepiandrosterone sulfate (DHEAS) was low normal (109.6 µg /dl with normal range: 98-340 microgram/dl).

The first impression was ACTH-independent Cushing syndrome. Thoracic and Abdominal computed tomography scan (CT-Scan) was unremarkable. Adrenal CT-Scan showed normal size adrenals without adenomas or suspicious lesions. Pituitary Magnetic Resonance Imaging (MRI) revealed a pituitary microadenoma, described as a tiny hypo intense area with 3 mm diameter in inferior and left side of sella turcica, which was enhanced with gadolinium. She had normal abdominal,

adrenal and pelvic MRI study. She also had unremarkable cardiac echocardiography and thyroid ultrasound. We performed Liddle's test (Sequential low-dose-high-dose dexamethasone suppression test) basal 24-hours urinary cortisol level (day 0) was 2000 µg and after LDDST and HDDST reached to 738 (day2), 854 (day4) and 1146 (day6) µg, respectively. No paradoxical increase in urinary cortisol level was observed.

Patient was candidate for sequential bilateral adrenalectomy. She underwent left adrenalectomy first. On the first postoperative day, serum cortisol level at 8A.M was 12.45 µg/dl. The left adrenal gland dimension was 5.1×3×4 cm with 15 grams weight. The pathology showed increase in the thickness of reticularis and fasciculate layers. There were an abundant of clear cells with eosinophilic cytoplasm and most of them had brown pigments, which represent pigmented nodular adrenal hyperplasia (PNAH). Post-surgery, she had lower blood pressure and needed adjustment of antihypertensive medications (three medications). She had lost 5kg weight. However, other symptoms such as hirsutism, abnormal menstruation and central obesity persisted and serum cortisol level at 8 PM was 14.4 µg/dl. Six months later, after a discussion regarding the benefits and risks of bilateral adrenalectomy, she agreed with proceeding toward right adrenalectomy. She had received right adrenalectomy, which led to 10 kg more weight loss. Her blood pressure and menstrual cycle improved. She was started on hydrocortisone and fludrocortisone postoperatively. Her serum cortisol level reached to 3 µg/dl after holding hydrocortisone for 24 hr. The right adrenal gland dimension was 2×2×7 cm with 26 grams weight. The pathology was consistent with PPNAD.

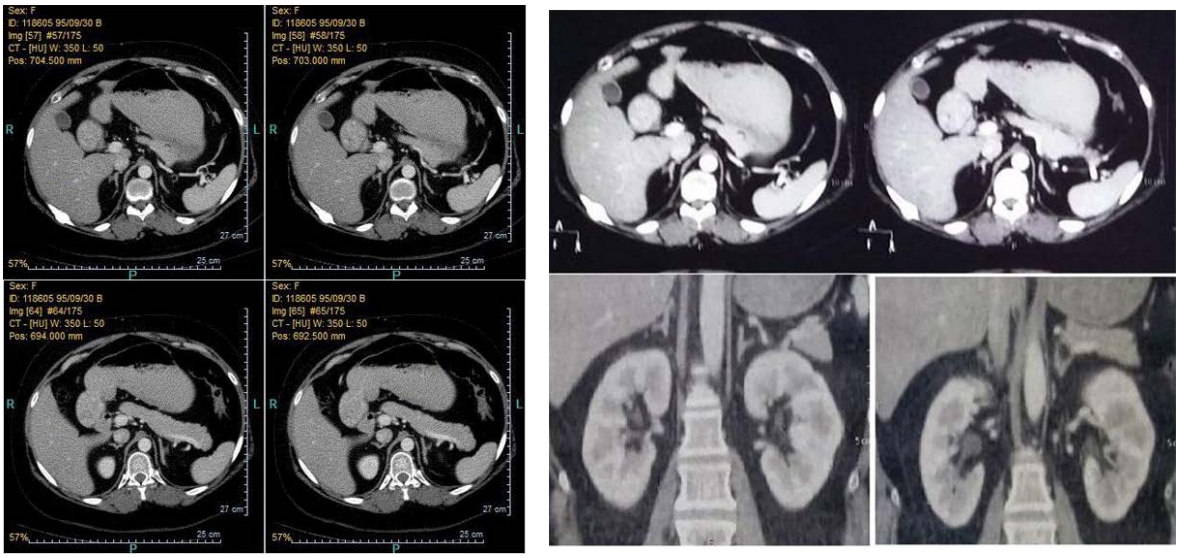

Figure 1. Left: Normal right and left adrenal MRI. Right: Normal right and left adrenal CT scan

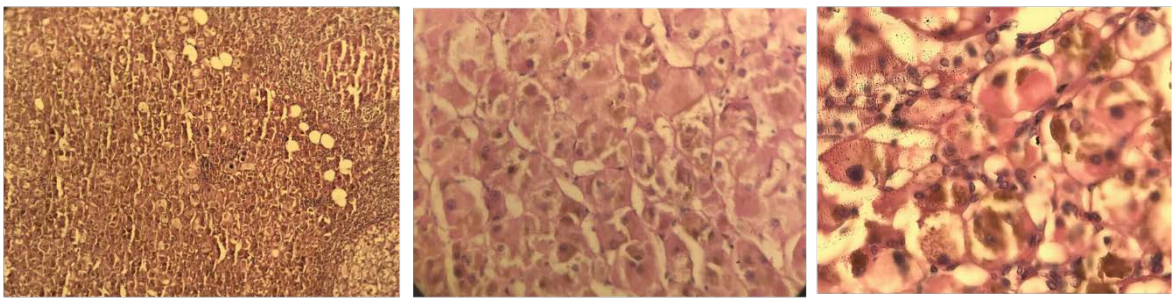

Figure 2. A: Nodular growth pattern of adrenocortical epithelial cells (Low power field, x 100, H&E staining) B: Proliferation of both clear and eosinophilic epithelial cells (x200, H&E staining) C: Eosinophilic cells contained brownish pigments together with others showing clear cytoplasm and nuclear aberrations (x400, H&E staining)

3. Discussion

PPNAD is a rare cause of ACTH-independent Crushing's syndrome. Overall, 25-30% of PPNAD patients will develop Cushing's syndrome. The usual time of presentation of PPNAD is in the second decades of life and rarely manifests in younger than four or older than 40 years old [7,8]. PPNAD is more common in women than in men after adolescence. It is usually asymptomatic and diagnosis made by taking familial history and biochemical workups, include low dose and high dose dexamethasone suppression tests [9].

The current case had symptoms and signs of Cushing syndrome but imaging studies, such as CT and MRI, could not determine the source of cortisol production. Therefore, the decision of interdisciplinary conference was to proceed with sequential bilateral adrenalectomy. Pathology report of resected adrenal confirmed PPNAD diagnosis even though we did not observe the paradoxical increase in urinary cortisol level after LDDST and

HDDST. However, around 69 to 75% of PPNAD patients will have a paradoxical rise in urinary cortisol excretion after LDDST and HDDST. Furthermore, adrenal imaging with CT or MRI may not be able to detect abnormalities in adrenal gland.

Diagnosis of these rare conditions are challenging as imaging modalities and biochemical workups are not always conclusive and histological evaluation requires surgical intervention. The gross and histological appearance of PPNAD is characteristic, and genetic studies are not usually necessary for diagnosis. Sometimes, we should monitor the patient closely for the possible development of PPNAD and high clinical suspicious is required to prompt diagnosis.

Carney complex Syndrome is as autosomal dominant disorder belongs to a familial multiple endocrine neoplasia syndrome that can present with different tumors, such as cardiac and cutaneous myxoma, lentiginous and endocrinopathy, including PPNAD [10]. For clinical diagnosis of CNC, we must had at least familial history of CNC or two clinical CNC characteristics [11]. The recent case had normal thyroid function and ultrasound, and unremarkable echocardiography. She had pituitary microadenoma with no significant abnormal findings in abdomen and pelvic MRI. Although, she does not fulfill the diagnostic criteria for CNC, but she may develop some in future. Therefore, lone-term follow up is necessary.

In conclusion, the presentation of Carney complex could be variable among patients. Additionally, the recognition of ACTH-independent Cushing's syndrome can be difficult too, especially in patients with cyclical hypercortisolism. In most cases, removal of the bilateral adrenal glands is required to avoid complications of hypercortisolism. Patients should also be screened for cardiac myxoma periodically to prevent sudden unexpected death. The patients need long-term follow-up as the early diagnosis of other associated tumors improves outcomes. Finally, the health care providers should be aware of the various components of CNC to identify affected patients and screen their relatives, mainly first-degree relatives, appropriately.

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