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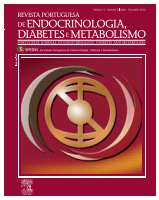

Caso Clínico

Giant Adrenal Adenoma Presenting as Cushing Syndrome

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A B S T R A C T

We present a case of a 37-years-old male with progressive facial flushing, hair growth in dorsal and lumbar back, easy bruising and diminished libido. The laboratorial workup revealed an adrenocorticotropic hormone-independent Cushing syndrome and elevated levels of testosterone, dehydroepiandrosterone sulfate and androstenedione. Computed tomography scan demonstrated a 10 cm, regular and well-defined lesion in the right adrenal with a heterogeneous pattern of density. The patient was submitted to a right adrenalectomy and the histological exam described a benign lesion without any Weiss criteria.

This case represented a clinical challenge due to the overlapping of biochemical and imaging characteristics that prevented a final pre-surgical diagnosis. As histologic criteria can be misleading, long-term follow-up is advisable. So far, the patient is asymptomatic without clinical evidence of hypercortisolism and/or hyperandrogenism.

Adenoma Adrenal Gigante como Manifestação de Síndrome de Cushing

Palavras-chave:
Adenoma Adrenocortical
Hiperandrogenismo
Neoplasias da Glândula Adrenal
Síndrome de Cushing

R E S U M O

Apresentamos um caso de um homem de 37 anos de idade com rubor facial progressivo, aumento de pilosidade dorso-lombar, equimoses fáceis e diminuição da libido. O estudo laboratorial revelou síndrome de Cushing independente de hormona adrenocorticotrófica e níveis elevados de testosterona, sulfato de dehidroepiandrosterona e androstenediona. A tomografia computadorizada demonstrou uma lesão de 10 cm na adrenal direita, de bordos regulares e bem definida e com um padrão de densidade heterogéneo. O doente foi submetido a adrenalectomia direita e o exame histológico revelou uma lesão benigna sem critérios de Weiss presentes.

Este caso representou um desafio clínico devido à sobreposição de características bioquímicas e imagiológicas que impediram um diagnóstico final pré-cirúrgico. Uma vez que os critérios histológicos podem apresentar falhas, o acompanhamento a longo prazo é aconselhável. Até agora, o doente está assintomático sem evidência clínica de hipercortisolismo e/ou hiperandrogenismo.

Introduction

Cushing syndrome (CS) is a rare disorder caused by prolonged exposure to excess glucocorticoids. It is associated to an increased morbidity and mortality due to the cardiovascular, thrombotic, metabolic, infectious and musculoskeletal complications.[1] Although the worldwide epidemiology has not been fully determined, it has an estimated prevalence of around 40 cases per million and an estimated incidence of 0.7 to 2.4 cases per million per year.[2,3]

CS clinical presentation reflects the consequences of body exposure to hypercortisolism, including nonspecific alterations such as obesity, hypertension, mood changes, and more unique signs such as proximal muscle wasting, round and erythematous face, cervical fat accumulation, purple striae and easy bruising. Signs and symptoms presentation and severity varies according to the extent and duration of cortisol excess. Typically, adrenocortical carcinoma is characterized by rapid attainment of very high cortisol levels and severe clinical signs while adenomas present a milder glucocorticoid hypersecretion and a more indolent course.[4]

CS englobes two main etiologies - adrenocorticotropic hormone (ACTH)-dependent (pituitary or ectopic ACTH secretion) and

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ACTH-independent (adrenal disorders). Adrenal causes of CS include both tumoral and genetic disorders. Tumors arising from the zona fasciculata of the adrenal cortex are responsible for 20% of endogenous CS in adults. Two-thirds of these neoplasms are adrenal adenomas and the remainder adrenocortical carcinomas. Age and gender distribution vary slightly between the different adrenal etiologies of CS, with adrenal adenoma occurring mostly in young adults and females.[5]

In adrenal CS, autonomous cortisol secretion by the adrenal glands will inhibit corticotropin releasing hormone (CRH), vasopressin and ACTH secretion. Measurement of serum dehydroepiandrosterone sulfate (DHEAS), testosterone, androstenedione and 17-hydroxyprogesterone (17-OHP) may aid in the distinction between benign and malignant adrenal tumors, as they are commonly low in adrenal adenoma and elevated in adrenal carcinoma.[5]

Although the clinical and chemical features may aid in differential diagnosis, there is a wide overlap between adrenal adenoma, carcinoma and hyperplasia. Accordingly, the etiology of adrenal CS is usually established by imaging of the adrenal glands. Adrenal tumors are easily detectable on computed tomography (CT) and/or magnetic resonance imaging (MRI) and the imagiological characteristics permit, in most of the cases, to differentiate the two entities. On CT images, an adrenal adenoma is suggested by the presence of a regular border, a maximum size measurement less than 4 cm, homogeneity of the lesion and an unenhanced density of less than 10 Hounsfield units (HU). Also, pre-contrast attenuation value of less than 10 HU on CT is suggestive of a lipid-rich tumor composed of benign steroidogenic cells. It has been demonstrated that a pre-contrast density below 10 HU has 98% specificity to diagnose an adenoma with a sensitivity of 71%. Approximately 30% of adrenal adenomas are lipid-poor, resulting in a higher pre-contrast attenuation value, which accounts for the lower sensitivity. However, many of these lipid-poor adenomas will be identified by rapid washout after contrast administration.[6] In contrast, adrenocortical carcinomas are typically larger, often show evidence of necrosis on enhanced CT scans and have poor contrast washout because of capillary leakage. Also, they frequently present with spread to adrenal or renal veins and distant metastatic disease.[7]

Currently, no single imaging method can determine unequivocally a localized adrenal mass as an adrenocortical carcinoma. It has been shown that positron emission tomography with 18fludeoxyglucose (18FDG-PET) is highly valuable in patients with suspected carcinoma undetermined by conventional imaging as high uptake of 18FDG indicates malignancy. However, some benign adenomas or pheochromocytomas also show uptake of 18FDG.[8]

An accurate diagnosis is critical, because the prognosis, follow-up and therapeutic strategy for adrenocortical carcinomas are very different from an adrenal adenoma. Nevertheless, it is difficult in some cases to distinguish malignant from benign cortical tumors accurately through clinical characteristics or histological criteria. Although data generated by molecular genetic techniques has undoubtedly made important contributions to the pathologic evaluation of adrenocortical neoplasms, at present, histologic assessment as defined by the Weiss system remains the mainstay for the diagnosis of adrenocortical carcinoma in the adult population.[9,10] However, score systems have pitfalls and it has been published that up to 9% of the original adrenocortical tumors pathologic diagnosis were changed upon revision.[11]

Case Report

A 37-year-old male with a 7-year history of hypertension and unexplained erythrocytosis was referred to our Endocrinology department due to suspected hypercortisolism. He reported progressive facial flushing, hair growth in dorsal and lumbar back, easy bruising and diminished libido for 4 years.

He was medicated with nebivolol 2.5 mg/day, telmisartan 80 mg/day and chlorthalidone 12.5 mg/day. The patient denied taking medication with corticosteroids.

On physical examination, he was overweight (body mass index of 26 kg/m2) and hypertensive. Also, he had rounded face, facial plethora, frontal alopecia, cervical fat pad and ecchymosis on right limb.

Investigations

The laboratory workup revealed an elevated 24-hour urinary cortisol (4004.76 ug/24h; NR: 55.5–286.6 ug/24h), a non-detectable ACTH (< 5.0 pg/mL; NR: < 46 pg/mL) and a non-suppressible cortisol secretion after 1 mg dexamethasone suppression (31.02 ug/dL). Loss of circadian pattern cortisol secretion was confirmed (27.41 ug/dL in early morning and 28.55 ug/dL at midnight).

Total testosterone (943.59 ng/dL; NR: 241–827 ng/dL), dehydroepiandrosterone sulfate (DHEA-S) (1763.00 ug/dL; NR: 80–560 ug/dL), androstenedione (> 10.0 ng/mL; NR 0.6–3.1 ng/

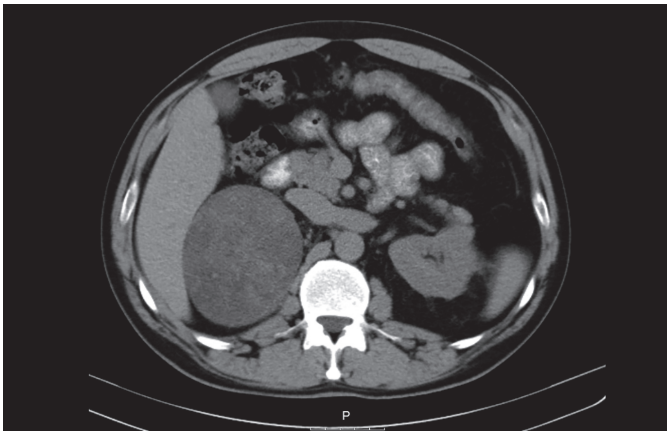

Figure 1. Non-contrast CT scan showing right adrenal mass with 10 cm maximum diameter (transverse section)

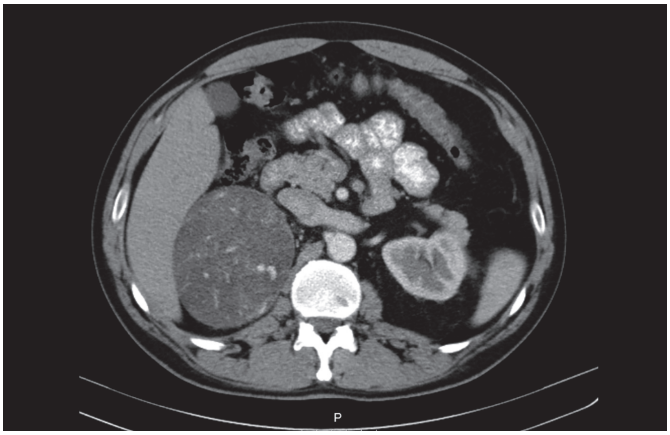

Figure 2. CT scan contrast-enhancing showing right heterogeneous adrenal mass with 10 cm maximum diameter (transverse section)

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mL) and 17-hydroxyprogesterone (17-OHP) (6.27 ng/mL; NR: 0.48–3.5 ng/mL) were elevated. Estradiol levels were in the upper limit value (149.26 pmol/L; NR: <146.1 pmol/L). Aldosterone, renin, urinary catecholamines and metanephrines and thyroid function were normal.

The abdominal CT scan showed a 10 cm length lesion in the right adrenal with regular and well-defined borders (Fig.s 1, 2 and 3). The lesion was heterogenous with slightly denser areas and others with low density, even with some negative attenuation values, however the reported density was 13 Hounsfield units (HU). After intravenous contrast injection, multiple vessels gained contrast within the nodule areas and there were areas with slight contrast gain and others remained hypodense, admitting the possibility of necrotic areas. The delayed contrast washout was inferior to 50%. No calcifications were visualized.

Treatment

The patient was submitted to a laparoscopic right adrenalectomy without complications. The histological examination described a capsulated nodular formation of 359 g and 10.5 x 7.5 x 6.9 cm length. The outer surface was smooth and was partly surrounded by adipose tissue. It was soft, yellowish and compact. The neoplasm was composed of nests of large cells with rounded, irregular and hyperchromatic nucleus. Some nucleoli were visible. The cytoplasm was ample and clarified (> 25% of all cells) or eosinophilic and with well-defined limits. Polymorphism was focally marked. The maximum number of observed mitotic figures was 2 per 50 fields of high amplification. Figures of atypical mitosis, capsule invasion, venous invasion and tumor or sinusoidal type of necrosis were not observed. The proliferative index (Ki67) was very low (< 1%).

Outcome and follow-up

The patient started glucocorticoid replacement in the perioperative period and, despite the gradual decrease in hydrocortisone dosage, he persistently complained of fatigue for about twelve months. Eighteen months after surgery, the pituitary-adrenal axis has recovered, and he stopped hydrocortisone treatment. Two years after surgery he is asymptomatic, and the levels of cortisol and androgen are normal. The arterial blood pressure is controlled without drugs and he has lost 10 kg.

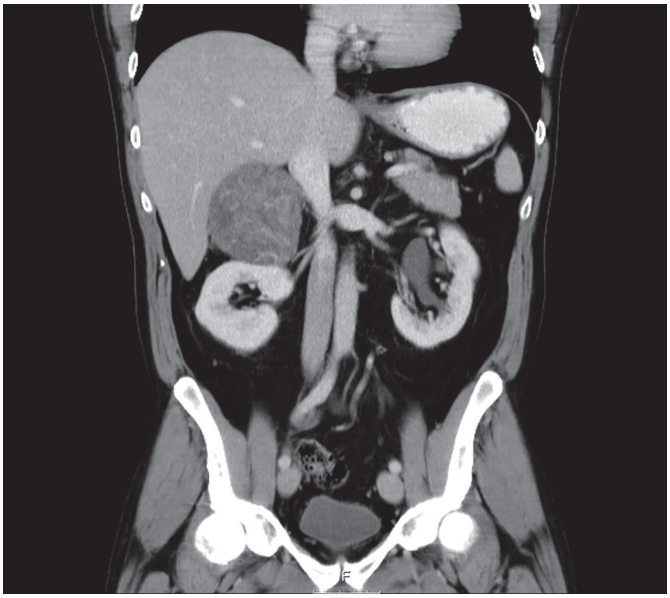

Figure 3. CT scan contrast-enhancing showing right heterogeneous adrenal mass with 10 cm maximum diameter (coronal section)

Discussion

Adrenal adenomas secreting both cortisol and androgens have been described, however tumor dimensions reported were up to 6 cm.[12–15] To our knowledge this is the first case report of a giant benign adrenal adenoma secreting both cortisol and androgens.

This case represented a challenge for the differential diagnosis between adrenal adenoma and carcinoma.

Despite the parallel in clinical and biochemical features between adrenal adenoma and carcinoma, serum androgens concentrations are generally subnormal in patients with adrenal CS caused by benign adenomas. In contrast, androgen hypersecretion in patients with CS is usually indicative of malignancy.[5,16] The reduced adrenal androgen synthesis in these patients results from pituitary ACTH secretion suppression by chronic hypercortisolism. This leads to atrophy of both peritumoral adrenocortical tissue and the cortex of the contralateral adrenal gland. Therefore, there is a reduction of androgenic steroidogenesis in those tissues. Conversely, carcinomas often secrete a combination of cortisol and androgens and their precursors.[5,8,16]

However, it has been described that hormonal concentrations have a limited value in predicting malignancy and adrenal adenomas can also produce testosterone, DHEA-S and androstenedione.[5,16,17] Kamenicky and his colleagues have demonstrated that patients with cortisol secreting adenomas also secrete small amounts of androgens that normalized after removal of the tumor.[16] Previously, Sakai *et al* have suggested that the high levels of adrenal androgens in patients with adrenal CS secondary to benign cortical adenomas may be explained by high concentration of cytochrome b5.[18] Cytochrome b5 plays an important role in determining the activity ratio of CYP17 towards 17,20-lyase activity, expressed in the zona fasciculata and reticularis of the adrenal cortex, promoting the adrenal androgen production.[19,20] Other key enzymes involved in adrenal androgenic steroidogenesis is *SULT2A1* and *HSD3B2*, which are both expressed in cortisol-producing tumors.[16] The former converts DHEA into DHEA-S in the zona reticularis and the latter catalyzes the conversion of 3β-hydroxy-5-ene steroids to 3-keto-4ene steroids, permitting the adrenal gland to synthesize progesterone and 17-OHP in the zona fasciculata and androstenedione (from DHEA) in the zona reticularis of the adrenal cortex.[19]

The described adrenal lesion presented imagiological characteristics that favored a benign lesion such as the regular and well-defined borders, the presence of negative attenuation values regions and the absence of calcifications. Moreover, the lesion did not invade adjacent structures and no lymph nodes were visualized. Although, the size of the lesion and the presence of multiple vessels that captured contrast and the poor contrast washout associated with capillary leakage could predict a malign lesion. The heterogeneity of the mass due to intra-tumoral necrosis or cystic degeneration while extremely frequent in adrenocortical carcinoma, may be encountered also in degenerated adenomas, so are not absolute criteria.[21]

Although without a definitive pre-surgical diagnosis, the patient was submitted to a right adrenalectomy. The benign nature of the lesion, demonstrated by the absence of Weiss criteria in histological examination, guided the subsequent management. However, according to the published literature, scoring system as

Weiss criteria can be misleading. The patient maintains regular follow-up visits with hormonal measurements to assure disease remission.

Conclusion

This case represents the first described case of Cushing syndrome and hyperandrogenism caused by a benign 10 cm adrenal lesion with potential malign characteristics in laboratory and imagiological workup.

The authors intent to recall that hormonal measurements and tumor size are important markers of the potential malignancy of adrenal masses, but the definitive diagnosis is made by histological examination. However, histologic criteria can be misleading in these lesions and long-term follow up is advisable.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação dos dados de doentes.

Ethical Disclosures

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Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.

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