Giant adrenal myelolipoma associated with 21-hydroxylase deficiency: unusual association mimicking an androgen-secreting adrenocortical carcinoma

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SUMMARY

The objective of this study was to describe a case of giant myelolipoma associated with undiagnosed congenital adrenal hyperplasia (CAH) due to 21-hydroxylase (21OH) deficiency. Five seven year-old male patient referred with abdominal ultrasound revealing a left adrenal mass. Biochemical investigation revealed hyperandrogenism and imaging exams characterized a large heterogeneous left adrenal mass with interweaving free fat tissue, compatible with the diagnosis of myelolipoma, and a 1.5 cm nodule in the right adrenal gland. Biochemical correlation has brought concerns about differential diagnosis with adrenocortical carcinoma, and surgical excision of the left adrenal mass was indicated. Anatomopathologic findings revealed a myelolipoma and multinodular hyperplasic adrenocortex. Further investigation resulted in the diagnosis of CAH due to 21OH deficiency. Concluded that CAH has been shown to be associated with adrenocortical tumors. Although rare, myelolipoma associated with CAH should be included in the differential diagnosis of adrenal gland masses. Moreover, CAH should always be ruled out in incidentally detected adrenal masses to avoid unnecessary surgical procedures. Arq Bras Endocrinol Metab. 2010;54(4):419-24

SUMÁRIO

O objetivo deste trabalho foi descrever um caso de mielolipoma gigante associado à hiperplasia adrenal congênita (HAC) por deficiência da 21-hidroxilase (21OH). Paciente do sexo masculino, 57 anos de idade, encaminhado por achado ultrassonográfico de massa adrenal esquerda. Investigações bioquímicas revelaram hiperandrogenismo e exames de imagem revelaram grande lesão sólida em adrenal esquerda de aspecto heterogêneo, entremeado de tecido gorduroso, compatível com diagnóstico de mielolipoma, e um nódulo de 1,5 cm na adrenal direita. Os achados bioquímicos sugeriam o diagnóstico de carcinoma adrenocortical, indicando cirurgia para retirada da massa adrenal esquerda. O anatomopatológico confirmou mielolipoma e hiperplasia multinodular do córtex adrenal. A investigação subsequente diagnosticou HAC por deficiência da 21OH. Concluiu-se que a HAC tem sido descrita em associação com tumores adrenocorticais. Apesar de raro, o mielolipoma associado à HAC deve ser incluído nas possibilidades diagnósticas de massa adrenal. Adicionalmente, a HAC deve ser sempre afastada nos casos de massa adrenal de achado incidental, evitando cirurgias desnecessárias. Arq Bras Endocrinol Metab. 2010;54(4):419-24

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INTRODUCTION

Adrenal myelolipomas are relatively uncommon benign tumors, usually small and unilateral. They are usually found incidentally and rarely present as giant myelolipomas (1). They are composed of mature adipose cells and haematopoietic myeloid cells (2,3). Although usually asymptomatic, myelolipomas can cause pain upon the occurrence of hemorrhage, necrosis or compression. Occasionally, they can occur concomitantly with other lesions such as cortical adenoma (2-4), ganglioneuroma (5), carcinoma (6), pheochromocytoma (7), or CAH (8). Although characteristically non-functioning, there have been a few reports of myelolipomatous masses associated with adrenocortical hypersecretion (8,9). On radiologic evaluation, they typically present a high fat content that gives them a pathognomonic appearance on CT and MRI images (10,11). On CT, the presence of low attenuation fat in the lesion, which has a density of -30 HU, is a specific and diagnostic finding. On MRI, the fat components in the lesion demonstrate high signal on T1- and T2-weighted images and lose signal on T1-fat-saturated images resembling intra-abdominal fat (10,12). However, the presence of hemorrhage and necrosis features can emulate the radiological aspect of adrenocortical carcinoma (10).

In this report, we describe an uncommon case of a 57-year-old man with a giant myelolipoma presented as an adrenal mass with a heterogeneous appearance on radiologic evaluation associated with hyperandrogenism resulting in preoperative diagnosis of adrenocortical carcinoma. The anatomopathologic findings revealed a myelolipoma, and further investigation resulted in the associated diagnosis of CAH due to 21OH deficiency.

CASE REPORT

A 57-year-old Brazilian male patient was referred to the Endocrine Division in June 2008 with abdominal pain and an abdominal ultrasound revealing a left adrenal mass of 12 x 9 x 12 cm. He was father of two daughters aged 32 and 34 years. At admission, the patient weighed 56.8 kg and was 160 cm tall, with a body mass index of 22 kg/m². He had a blood pressure of 100/70 mmHg and a heart rate of 72 beats/min. Other physical examination was unremarkable, except by slightly decreased and hard testis (3.5 x 2 cm bilaterally). There was no clinical evidence of Cushing’s syndrome, hyperaldosteronism or pheochromocytoma. A laboratory screening for adrenal incidentaloma demonstrated suppressed plasma cortisol levels after 1 mg overnight dexamethasone (33 nmol/L; normal < 50); normokalemia (4.3 mmol/L; normal range 3.5-5); normal urinary metanephrines (502 nmol/24h; normal range 31-1167) and urinary normetanephrines (1147 nmol/24h; normal range 240-2459), and plasma catecholamines (3.6 nmol/L; normal range 0.7-3.9); normal DHEAS (4 μmol/L; normal range 6.5-9.1); normal testosterone (13 nmol/L; normal 8.7-31.2 range), and elevated androstenedione (74 nmol/L; normal range 2.1-8.7). CT and MRI exams have characterized the lesion as a large heterogeneous left adrenal soft tissue mass with substantial amount of interweaving free fat tissue. There was also a 1.5 cm nodule with similar features in the right adrenal gland (Figure 1).

Although the imaging features were typical for myelolipoma, the biochemical findings showing androstenedione hypersecretion associated with a large adrenal mass led to a preoperative diagnosis hypothesis of androgen secreting adrenocortical carcinoma. Patient underwent open left adrenalectomy. The intraoperative findings demonstrated a 15 x 10 cm left adrenal circumscribed mass which was completely excised, and a small pigmented right adrenal mass of around 1.5 cm, that was not removed due to its benign appearance. Pathological findings revealed an enlarged left adrenal gland with a yellow and tan circumscribed mass of 15 cm in its largest diameter that weighed 585 g. At the microscopy the tumor was characterized as a myelolipoma that rose on a multinodular hyperplasic adrenocortex (Figure 2).

The patient postoperative recovery was unremarkable, but the androgens remained elevated on the fifth day after surgery (Table 1). To rule out a potentially unsuccessful surgery and to diagnose a suspected CAH, measurement of basal and post ACTH1-24 stimulation test 17OHP was performed, followed by a 2 mg/day dexamethasone suppression test during 5 days. Basal 17OHP was 261 nmol/L, reaching 342 nmol/L 60 minutes after ACTH1-24 (Table 1). All androgens showed a marked suppression after 5 days of the dexamethasone suppression test, thus confirming the diagnosis of CAH (Table 1).

To further confirm CAH diagnosis, a genomic analysis was performed from the DNA of the peripheral blood leukocytes and the patient was found to be a compound heterozygous carrier of the Q318X and intron2 splicing (Sp2) mutation in the CYP21A2 gene. Later on, therapy was initiated with 5 mg of prednisone and 0.1 mg of fludrocortisone daily, with the androste-
nedione level falling into normal range (Table 1). A low testosterone level (3.2 nmol/L) and slightly high levels of LH and FSH (20 and 13.2 IU/L, respectively), indicate an actual primary gonadal dysfunction most likely due to long-term suppression of hypothalamic-pituitary-gonadal axis.

**DISCUSSION**

The pathogenesis of adrenal myelolipomas remains unclear. A variety of mechanisms are proposed to underlie the etiology of adrenal myelolipomas, such as the presence of embryonic bone marrow in adrenal tissue (3). Some evidences indicate that ACTH may have a role in the development of these tumors, demonstrated by an increase in the relative frequency of myelolipomas in patients with excessive ACTH secretion, such as in CAH (13,14), Nelson’s syndrome (15), and Addison’s disease (3). Moreover, myeloid metaplasia in the adrenal cortex is observed in severely burned and cancer patients, two groups that are subject to long periods of intense stress (16). Indeed, myelolipomas have been associated with various forms of CAH like 21OH deficiency, 17-hydroxylase (17OH) deficiency and recently with 11β-hydroxylase deficiency (17). It is worth pointing out that most of these patients were either untreated or had stopped taking their medication for an extended period and were exposed for many years to chronically elevated ACTH and androgen levels which have been shown to induce transformation of adrenal cortical precursor cells into mature fat cells (17,18).

To date, approximately 25 cases of myelolipomas associated with CAH have been reported. The mean age of these patients was 48 years (range 23-82 years). The characteristics of each patient and tumor are shown in table 2. The majority of them, 19 (76%), was associated with CAH due to 21OH deficiency, 4 (16%) with CAH due 17OH deficiency and 1 (4%) with CAH due to 11β-hydroxylase deficiency. Our patient presents CAH due to 21OH deficiency, with a genotype Q318X / Sp2. Considering size and localization, the mean tumor size was 12.4 cm (range 1-43 cm) and bilateral lesions were reported in ten cases (40%). Jaresch and cols. (37) previously described a positive correlation between the age of CAH patients and the age at onset of therapy, and adrenal size; with older patients and patients who were untreated for a long period presenting the most hyperplastic adrenal glands with no correlation between tumor size and serum 17OHP concentrations. In these cases, chronic ACTH excess could induce diffuse or nodular adrenocortical hyperplasia which would later become autonomous because of oncogenic mutations in the tissue. Although under-diagnosis of CAH due to 21OH deficiency is more frequent in male patients, as observed in our case, there was no difference in gender prevalence of myelolipomas associated with CAH des-
Table 1. Basal hormone concentrations before, after surgery and under treatment with prednisone (5 mg daily) associated with fludrocortisone (0.1 mg daily). Dexamethasone suppression test and ACTH1-24 stimulation test performed after surgery.
In conclusion, we describe a rare case of giant myelolipoma associated to CAH due to 21OH deficiency. The excessive ACTH and/or androgen secretion over a long period of time could have had a stimulatory role in the development of the adrenal myelolipoma in the present patient. However, the mechanism underlying the reduced 21OH reserve among incidentaloma patients and the increased occurrence of adrenal tumors in simple virilizing or late-onset CAH forms remains a matter of speculation. Additionally, although surgery was mandatory in the present case due to tumor symptoms and size, CAH should always be ruled out in incidentally detected adrenal masses to avoid unnecessary surgical procedures.

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