

Bilateral giant adrenal myelolipoma associated with congenital adrenal hyperplasia

Mielolipoma adrenal gigante bilateral associado a hiperplasia adrenal congênita

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ABSTRACT

Adrenal myelolipomas are rare benign tumors, often non-functioning, located in the adrenal cortex, consisting mainly of mature adipose tissue and hematopoietic tissue. Although uncommon, the number of reported cases has increased due to the greater use of diagnostic imaging techniques. This tumor is usually unilateral and found as an adrenal incidentaloma, although there is a predominance of bilaterality in patients with congenital adrenal hyperplasia (CAH). In this study, we report the case of a 33-year-old male patient with CAH due to 21-hydroxylase deficiency, in non-regular use of the control medication, with bilateral giant adrenal myelolipoma and subsequent evolution of bilateral testicular adrenal rest tumors. He underwent bilateral adrenalectomy by video laparoscopy. The anatomopathological analysis, which confirmed myelolipomas' diagnosis, revealed the right adrenal with 430 g and 12.5 x 9.3 cm and the left with 257 g and 11.5 x 10.4 cm. This tumor may be accompanied by adrenocortical adenoma and carcinoma, ganglioneuroma, pheochromocytoma, Addison's disease, Cushing's syndrome, or CAH. Among the hypotheses of its pathogenesis, we highlight an association between the development of adrenal myelolipoma and chronic hormonal stimulation by the adrenocorticotrophic hormone (ACTH), especially in CAH. The non-regular treatment of CAH with glucocorticoids may have contributed to the chronic and elevated secretion of ACTH and, consequently, to the development of bilateral giant adrenal myelolipoma.

Keywords: Myelolipoma, Congenital adrenal hyperplasia, Adrenocorticotrophic hormone.

RESUMO

Mielolipomas adrenais são tumores benignos raros, com frequência não-funcionantes, localizados no córtex da adrenal, constituídos, principalmente, por tecido adiposo maduro e tecido hematopoético. Apesar de incomum, o número de casos relatados tem aumentado devido ao maior uso de técnicas diagnósticas de imagens. Esse tumor é geralmente unilateral e encontrado como um incidentaloma adrenal, embora haja predominância de bilateralidade em casos de portadores de hiperplasia adrenal congênita (HAC). Neste estudo, relatamos o caso de um paciente do sexo masculino, de 33 anos, portador de HAC por deficiência de 21-hidroxilase, em uso não-regular da medicação de controle, com mielolipoma adrenal gigante bilateral e posterior evolução de tumor bilateral testicular de restos de adrenais. Ele foi submetido à adrenalectomia bilateral por videolaparoscopia. A análise anátomo-patológica, que confirmou o diagnóstico de mielolipomas, revelou adrenal direita com 430 g e 12,5 x 9,3 cm, e esquerda com 257 g e 11,5 x 10,4 cm. Esse tumor pode vir acompanhado de adenoma e carcinoma adrenocortical, glanglioneuroma, feocromocitoma, doença de Addison, Síndrome de Cushing ou HAC. Dentre as hipóteses de sua patogênese, destacamos uma associação entre o desenvolvimento do mielolipoma adrenal e a estimulação hormonal crônica pelo hormônio adrenocorticotrófico (ACTH), especialmente na HAC. O tratamento não-regular da HAC com glicocorticoides pode ter contribuído para a secreção crônica e elevada de ACTH e, conseqüentemente, para o desenvolvimento do mielolipoma adrenal gigante bilateral.

Palavras-chave: Mielolipoma, Hiperplasia adrenal congênita, Hormônio adrenocorticotrófico.

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INTRODUCTION

Myelolipomas are rare benign tumors located in the cortex of the adrenal gland and, in most cases, endocrinologically inactive¹. In the past, its diagnosis usually occurred during the autopsy, but today, non-invasive diagnostic imaging techniques have increased the incidental detection of adrenal tumors². Its occurrence can be concomitant with other lesions, such as cortical adenoma³, ganglioneuroma⁴, adrenocortical carcinoma⁵, or congenital adrenal hyperplasia (CAH)⁶. A study of a large group of non-selected patients with 21-hydroxylase deficiency reported an adrenal myelolipoma frequency of about 4%⁷. On the other hand, about 10% of myelolipoma cases are associated with CAH, while other hypersecretory adrenal disorders are present in 7.5% of cases^{8,9}. Finally, these tumors are rarely giant⁷, but cases of bilateral giant adrenal myelolipomas associated with CAH have been described^{2,5,6,10-12}.

This report describes an unusual case of giant bilateral adrenal myelolipoma in a 33-year-old male patient with CAH due to 21-hydroxylase deficiency, diagnosed in childhood, with a history of irregular use of the control medication. Later, after investigating hypogonadism and reducing libido, he was also diagnosed with bilateral testicular adrenal rest tumors (TART).

CASE REPORT

The present case report was analyzed and approved by the Research Ethics Committee of the Federal University of Uberlândia under the CAAE (from the Portuguese *Certificado de Apresentação de Apreciação Ética*, meaning Ethical Appraisal Presentation Certificate) number 45482120.3.0000.5152 and the consubstantiated declaration number 4.750.419.

Brazilian male patient, 33 years old, with chronic renal failure, on hemodialysis, and CAH diagnosed at 28 days of life, caused by 21-hydroxylase deficiency and manifested in the salt-wasting form. With a documented history of precocious puberty, non-regular use of control medication (glucocorticoids), and adrenal decompensation – manifested by arterial hypotension – at 12 years

old, without follow-up from 16 to 33 years old, the patient was admitted to our service for bilateral adrenalectomy due to bilateral giant adrenal myelolipoma, which was performed without complications by video laparoscopy.

The lesions were found incidentally on abdominal computed tomography (CT) (Figure 1) requested by nephrology, with the initial impression of bilateral giant adrenal myelolipoma, and, after adrenalectomy, the anatomopathological analysis revealed grossly ovoid structures, surrounded by adipose tissue, covered by a thin gray capsule and with a cut surface showing yellowish areas, consistent with adipose tissue, and wine areas on macroscopic examination. The diagnosis was confirmed by microscopy. The right adrenal weighed 430 grams and measured 12.5 x 9.3 cm, while the left adrenal weighed 257 grams and measured 11.5 x 10.4 cm.

Preoperatively, the patient received 50 mg of intravenous (IV) hydrocortisone four times a day, gradually reducing it to two times a day postoperatively. On the 5th postoperative day, the medication was replaced by prednisone, 10 mg in the morning and 5 mg in the evening. That same day, the patient started using 0.1 mg/day of fludrocortisone, in addition to receiving, until the 8th postoperative day, 100 mg of IV hydrocortisone when presenting episodes of refractory hypotension. The patient also presented hyperkalemia, with serum potassium at 5.8 mEq/L (reference range: 3.5–5.5 mEq/L), and a tendency to hyponatremia, with serum sodium at 131 mEq/L (reference range: 130–146 mEq/L), both corrected with adjustment of the dose of fludrocortisone.

The patient progressed to hypogonadism with decreased libido and a decline in serum testosterone from 664.7 ng/dL before surgery, with undetectable LH and FSH values, to 160.7 ng/dL on the 8th day of postoperative when scrotal ultrasonography (USG) was requested for investigation. With normal serum levels of sodium (135 mEq) and potassium (4.3 mEq/L), without signs of arterial hypotension and clinically well, the patient was discharged on the 9th postoperative day, with oral use of prednisone (7.5 mg/day) and fludrocortisone (0.1 mg/day), and recommendation for IV administration of glucocorticoid in case of diarrhea or stress.

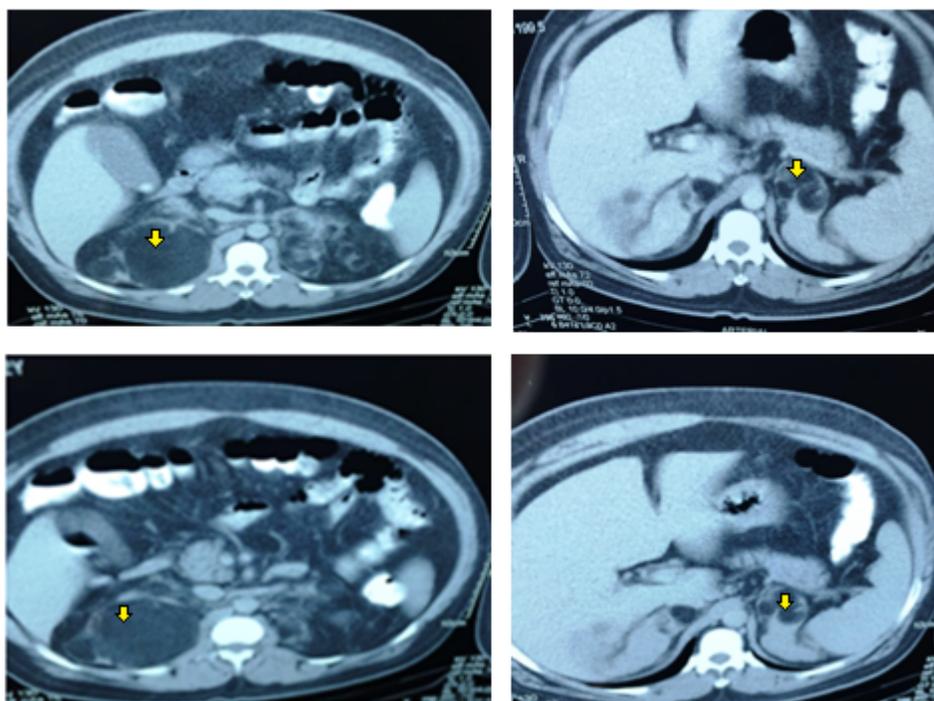


Figure 1: Axial sections of computed tomography of the abdomen showing, in the anatomical location of the adrenal glands, giant, bilateral, and homogeneous masses (with the left showing internal septations), with densities compatible with adipose tissue (arrows)

Ultrasound showed a diffuse alteration in the bilateral testicular texture suggestive of fibrosis, with parenchymal infiltration, in addition to solid, heterogeneous, non-capsulated masses, with unclear limits and with an arterial and venous flow at the Doppler study, in the right and left scrotum, of nonspecific origin.

Because of the ultrasound results, the patient was again hospitalized for biopsies, performed without complications with a fine needle. The microscopic and immunohistochemical findings, together with the clinical history and the bilaterality of the tumor, favored bilateral TART diagnosis.

DISCUSSION

Adrenal myelolipoma is a benign tumor of the adrenal cortex consisting mainly of mature adipose tissue and hematopoietic tissue and is included in the group of mesenchymal and stromal tumors of the adrenal cortex according to the latest update from the World Health Organization (WHO) on endocrine neoplasms⁸. In general,

it is non-functioning, small (≤ 4 cm), and asymptomatic^{1,2,5,8,13}, which justifies the fact that it is frequently (6 to 16% of these cases) found as an adrenal incidentaloma^{8,9}. In symptomatic cases, usually associated with larger tumors, manifestations include abdominal discomfort and distension, vomiting, pain, and, in more severe compressive conditions, hematuria, hydronephrosis, renovascular hypertension, retroperitoneal hemorrhage, and even hemodynamic shock^{1,2,5,8,14}.

Most of the time, it is unilateral, and the right side is more commonly affected⁸, except in the case of patients with CAH, in which bilaterality predominates, followed by the left and right sides, respectively, if unilaterally present. When bilateral, growth is usually asymmetrical, as the left adrenal myelolipoma supposedly would have more room to grow, while the right tumor growth would be restricted by the liver¹. Therefore, the first tends to be slightly larger than the second, but it is worth noting that this difference in size was not statistically significant⁸.

Despite being the most common fatty adrenal tumor, its occurrence is relatively rare, being

more frequent in the age group from 40 to 70 years old, with no preference regarding sex². On the other hand, there has been an increase in the number of reports, possibly due to the increased CT and magnetic resonance imaging (MRI) use^{1,5,8}.

Little is known about the pathogenesis of adrenal myelolipoma. However, several hypotheses have been raised, including chronic hormonal stimulation by adrenocorticotrophic hormone (ACTH) on mesenchymal cells of the adrenal cortex, with the development of pro-inflammatory adipose tissue, myeloid metaplasia, and recruitment of hematopoietic cells; the presence of remains of embryonic bone marrow in the adrenal; and bone marrow embolization to the adrenal^{1,2,5,8,9,13,15}.

In this sense, an association was observed between the development of adrenal myelolipoma and chronic states of elevated ACTH, especially in CAH, in which the presentation of bilateral and giant adrenal myelolipomas (≥ 8 cm), although rare, is more frequent compared to other groups studied¹³. This concomitance is present in the reported case, in which the treatment of CAH with glucocorticoids was done irregularly, which resulted in poor control of the disease and high ACTH levels in the patient in question. Association of myelolipomas with prolonged stress (diabetes mellitus, cancer, systemic arterial hypertension, obesity, and chronic inflammatory diseases)^{1,2,8}, and findings of myeloid metaplasia in the adrenal cortex of patients with cancer and/or severe burns were reported^{1,5}. This association was also reported in a case of lung carcinoma with excessive ectopic production of ACTH^{1,8}.

Additionally, the transactivation increase due to the androgen receptor (AR) gene polymorphisms and the hyperexpression of melanocortin 2 (MC2R) and androgen receptors in adrenal myelolipomas are among the main findings of a recent study. These actions mean ACTH and androgens can act as chronic stimulators of adrenal myelolipomas in patients with poorly controlled CAH¹³. Despite this, ACTH and androgens' roles in this tumor's origin and growth are controversial. The performance of these hormones, particularly ACTH, may be limited once some studies have found an absence of local hyperexpression of ACTH receptors^{1,8,13} and an association between adrenal myelolipoma and ACTH-independent Cushing's Syndrome¹.

Other conditions, such as adrenocortical adenoma, adrenocortical carcinoma, ganglioneuroma, pheochromocytoma, Addison's disease, Cushing's syndrome, and CAH, may accompany this tumor^{1,2,5,13}. About 10% of myelolipomas are associated with CAH, and 7.5% with other hypersecretory adrenal disorders (hypercortisolism, primary hyperaldosteronism, and others)^{8,9}. In this context, a potential confusion of injuries, concomitant or not, can hinder diagnosis and decision-making, revealing the importance of knowing more and drawing up guidelines about such a pathological entity⁸.

Regarding the radiological method, myelolipoma tends to have low attenuation (CT), hyperintense signal (MRI), and hyperechogenicity (USG), the greater the fat content of the tumor, and CT is considered the most sensitive imaging test for its diagnosis².

In pathological terms, this lesion usually has a thin capsule involving clusters of adipocytes and hematopoietic cells and, between them and on the periphery, some islands of adrenocortical cells, but it can also present hemorrhage, septations, fibrosis, hemosiderin deposition, calcification, and necrosis^{2,5,8}. Such adrenocortical components may have inadequate secretion of steroidal hormones, a condition usually associated with other diseases, including hypersecretion disorders in the adrenal cortex^{5,8}.

Faced with an adrenal myelolipoma, as there are no well-established and systematized guidelines in the scientific literature, the conduct is decided on a case-by-case basis⁸. In asymptomatic cases with lesions ≤ 4 cm, an expectant approach is generally adopted, with clinical observation and annual CT, under the benefit of avoiding long-term steroidal hormone replacement^{1,9}. Symptomatic tumors, functioning, if complicated with rupture and/or without exclusion of malignancy, must undergo surgery, regardless of the lesion size^{1,2,9}.

Still, regarding surgical indications, surgery is also recommended if the tumor size is larger than 7 cm due to the risk of spontaneous rupture and hemorrhage. However, some surgeons already indicate the procedure when the tumor is larger than 5 to 6 cm – since some adrenal neoplasms with malignant potential may present as non-functioning – or even when it is larger than 4 cm due to the risk of rupture – already present, albeit small

– and other associated complications¹. In the present case, the patient underwent bilateral adrenal-ectomy due to bilateral giant adrenal myelolipomas associated with poorly controlled CAH.

Fundamentally, the resection to be performed can be by open or laparoscopic surgery and is indicated when the risk of malignancy and/or spontaneous bleeding exceeds the surgical risk and the benefit of conservative management^{1,2,9}.

Among the study's limitations, it should be noted that the authors did not have access to the complete radiological report of the computed tomography or to the laboratory tests that characterize the hormonal status of CAH.

CONCLUSION

We describe and discuss a case of bilateral giant adrenal myelolipomas associated with CAH, a condition whose excessive secretion of ACTH and/or androgen for an extended period may have been a stimulator in the development and presentation of these lesions in the patient. Adrenal myelolipoma is an unusual and benign neoplasm of the adrenal cortex with adipose and hematopoietic tissue components and is often small, asymptomatic, incidental, and without hormonal activity. However, it gains importance when it is functional, complicated, symptomatic (due to compression and obstruction), and/or of large diameter – cases with indicated surgical intervention – and due to the generation of diagnostic difficulties in the face of other lesions, such as adrenocortical carcinoma so that detailed radiological (CT and/or MRI) and pathological information are of great help. The approach to be adopted in the face of adrenal myelolipoma should be more conservative or invasive, depending on its manifestations and size.

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Specific contribution of each author

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Participation in the drafting of the preliminary version: IMG, AMMC

Participation in the review and approval of the final version: PTJ, NPS, FTG

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