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CASE REPORT

Bilateral Testicular Adrenal Rest Tumor in a Young Adult with Poorly Controlled Congenital Adrenal Hyperplasia: Case Report

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Abstract

Congenital Adrenal Hyperplasia (CAH) is an autosomal recessive genetic disorder that affects adrenal steroidogenesis, compromising the production of hormones such as cortisol and, in some cases, aldosterone. More than 90% of cases are caused by a deficiency of the 21-hydroxylase enzyme, but rarer forms can occur due to the failure of other enzymes, such as 11β-hydroxylase or 3β-hydroxysteroid dehydrogenase. The reduction in cortisol synthesis leads to a chronic increase in adrenocorticotropic hormone (ACTH), due to the loss of negative feedback in the hypothalamic-pituitary-adrenal axis. This stimulates hyperplasia of the adrenal glands and excessive production of androgens. In male patients, a relevant complication is the development of Testicular Adrenal Rest Tumors (TARTs), with an average prevalence of around 40%, which can mechanically obstruct the seminiferous tubules and cause infertility. The treatment of CAH consists of chronic glucocorticoid replacement, with the aim of suppressing ACTH, reducing adrenal hyperplasia and preventing the growth of TARTs.

Resumo

A Hiperplasia Adrenal Congênita (HAC) é um distúrbio genético autossômico recessivo que afeta a esteroidogênese adrenal, comprometendo a produção de hormônios como o cortisol e, em alguns casos, a aldosterona. Mais de 90% dos casos são causados por deficiência da enzima 21-hidroxilase, mas formas mais raras podem ocorrer devido à falha de outras enzimas, como a 11β-hidroxilase ou a 3β-hidroxiesteroide desidrogenase. A redução na síntese de cortisol leva ao aumento crônico do hormônio adrenocorticotrófico (ACTH), pela perda do

feedback negativo no eixo hipotálamo-hipófise-adrenal. Isso estimula a hiperplasia das glândulas adrenais e a produção excessiva de andrógenos. Em pacientes do sexo masculino, uma complicação relevante é o desenvolvimento de Tumores de Restos Adrenais Testiculares (TARTs), com prevalência média em torno de 40%, os quais podem obstruir mecanicamente os túbulos seminíferos e causar infertilidade. O tratamento da HAC consiste na reposição crônica de glicocorticoides, com o objetivo de suprimir o ACTH, reduzir a hiperplasia adrenal e prevenir o crescimento dos TARTs.

INTRODUCTION

Congenital Adrenal Hyperplasia (CAH) is a group of autosomal recessive genetic conditions that affect steroid synthesis by the adrenal glands. Deficiency of the enzyme 21- hydroxylase is the most common cause, accounting for more than 90% of cases (1, 2), but there are less frequent forms caused by defects in other enzymes, such as 11β-hydroxylase, 17α-hydroxylase, 3β-hydroxysteroid dehydrogenase and 17, 20-lyase. This enzyme deficiency compromises the production of cortisol and, in some cases, aldosterone (2, 3, 4). As a result, the lack of cortisol activates a negative feedback mechanism, resulting in increased levels of adrenocorticotropic hormone (ACTH) by the pituitary gland (5, 4), leading to adrenal hyperplasia and overproduction of androgens (1).

An important complication in male patients, especially in the classic form of CAH, is the development of Testicular Adrenal Rest Tumors (TARTs) (6, 7, 8). Although these tumors are mostly benign (1, 6), their presence is associated with low fertility in affected individuals (9, 5). TARTs are formed by remnants of

adrenocortical tissue that have moved to the testes during embryonic development (8). Stimulated by high levels of ACTH, these adrenal remnants grow and multiply. In addition, the increase in luteinizing hormone (LH) during puberty is also suggested as a factor contributing to the growth of these lesions (1, 8).

TARTs are often bilateral and located within the rete testis (1, 7, 5). The main complication associated with these tumors is infertility, which occurs due to mechanical compression on the seminiferous tubules, especially when these masses reach a significant size. This type of damage can result in hypospermatogenesis or obstructive azoospermia, and irreversible damage to the testicles, such as peritubular fibrosis and tubular hyalinization, can persist even after the tumor formation has been removed (1, 8, 4).

Ultrasound is the most widely used imaging method to detect and monitor TARTs, due to its accessibility and efficiency in identifying lesions that are not yet palpable on physical examination. Typical features include bilaterality, good delimitation, location close to mediastinum testis, with hypoechogenicity and variable vascularization. An important factor in follow-up is the possibility of changes in the size or echogenicity of the lesions after starting treatment with glucocorticoids (1, 5, 4). Another challenge is the differentiation between TARTs and Leydig cell tumours (LCTs), since both have similar morphological characteristics. Histology and clinical context, such as a history of CAH and the bilaterality of the lesions, become fundamental for this distinction (1, 8, 4).

Treatment of TARTs focuses on controlling the underlying CAH and preserving reproductive function (4). The initial medical approach consists of glucocorticoid therapy in order to suppress ACTH production and promote a reduction in tumor size. However, the response to treatment is variable and does not always result in complete regression of the tumors or restoration of fertility. In selected cases, surgery may be well indicated, especially to relieve symptoms such as severe pain. However, early detection and strict hormonal control from childhood remain the main strategies for preventing permanent damage to the testicles and minimizing the reproductive consequences of this condition (8, 3, 4).

Considering the occurrence of TARTs in adolescents, their increased prevalence during puberty, the severity associated with inadequate hormonal control and the lasting impacts on gonadal function, it is essential to understand how this condition manifests itself and how it should be managed in this population.

CASE REPORT

Male patient, 24-year-old, Caucasian, currently on leave from his job as a security guard. He was followed up at the Endocrinology and Metabology outpatient clinic at the Federal University of Paraná, in Toledo - PR, due to congenital adrenal hyperplasia (CAH), diagnosed in childhood. Despite having undergone biological newborn screening (heel prick test) at the appropriate time, no alterations were identified. The first clinical signs appeared at 3 months of age, with pubic hair and penile enlargement, when treatment for the condition

was also started. There were no reports of perinatal complications associated with the condition. In terms of family history, a sister died at 45 days of age due to the classic form of CAH, with ambiguous genitalia and signs of dehydration.

Since the age of 8, the patient had been severely obese, weighing around 90 kg, and had been under continuous medical supervision. At the age of 14, he stopped treatment and his weight stabilized, with no evidence of clinical complications. At the age of 22, he was treated at another clinic and started taking prednisone 20 mg/day, fludrocortisone acetate 0.1 mg/day, spironolactone 25 mg/day and ketoconazole 200 mg/day. In October 2024, at the age of 23, he was seen at this outpatient clinic with grade 3 obesity, cushing's syndrome, obstructive sleep apnea and hypopnea syndrome (OSAHS), systemic arterial hypertension (SAH) and polyglobulia.

Physical examination revealed cushingoid facies, facial plethora, severe obesity (weight: 183 kg; height: 1.61 m; BMI: 70.60 kg/m²), cyanosis of the extremities, dorsal gibbosity, ochre dermatitis on the lower limbs and paronychia on both hallux. Evaluation of the genitals showed a 9 cm penis, topical testicles, painless on palpation, ultrasound with the presence of nodules suggestive of adrenal rests (hypoechoic, heterogeneous and infiltrative lesion in both testicles, without delimited borders, suggestive of TARTs).

On his return visit in 30 days, with tests results requested at the first appointment, the laboratory results showed hemoglobin (Hb) of 20.85 g/dL (VR: 13,5 - 17,5 g/dL), hematocrit (Ht) of 65.61% (VR: 41% - 50%), sodium of 139 mEq/L (VR: 135 - 145 mEq/L), potassium of 4.87 mEq/L (VR: 3,5 - 5,1 mEq/L), hormonal profile with cortisol of 2.27 µg/dL (VR: 3,7 - 19,4 µg/dL), ACTH of 56

pg/mL (VR: 9 - 52 pg/mL), androstenedione above 10 ng/mL (VR: 0,4 - 3,1 ng/dL), 17α-hydroxyprogesterone (17-OHP) of 10.000 ng/dL (VR: 50 - 210 ng/dL). With these data, the initial diagnosis of classic form CAH was confirmed. The therapeutic plan established included nutritional counseling, suspension of spironolactone, prednisone and fludrocortisone, associated with therapeutic phlebotomy and 11-deoxycorticosterone (DOCA) dosage, in order to allow for a subsequent diagnostic reassessment.

Approximately 60 days later, after therapeutic phlebotomy (2 sessions of 350 mL), a loss of 8 kg and blood pressure control with losartan and hydrochlorothiazide (50mg + 12.5mg), the patient reported clinical improvement, especially related to sleepiness. Baseline tests showed ACTH of 58 pg/mL, 17-OHP of 7,820 ng/dL, total testosterone of 251 ng/dL (VR: 249 - 836 ng/dL) and DOCA of 480 pg/mL (VR: ≤ 16 ng/dL), findings compatible with the classic form of non- salt-losing CAH, with a strong suspicion of 11β-hydroxylase deficiency. Repeated testicular ultrasound showed a bilateral tumor with slight progression. As a result, the prescrition included semaglutide (1.0 mg/week), prednisone was reintroduced at 2.5 mg/day and serial therapeutic phlebotomy was maintained (350 mL per session).

Four months after resuming drug treatment, laboratory tests revealed an Hb of 18.6 g/dL and Ht of 62%, total testosterone of 286 ng/dL and androstenedione above 10 ng/mL. During the same period, there was a weight loss of 13 kg, with a BMI of 65.58 kg/m². A repeat testicular ultrasound kept the findings unchanged. In view of this, the importance of adherence to prednisone therapy and maintenance of bloodletting was reinforced. The dose of

semaglutide was increased to 1.2 mg/week in order to optimize metabolic control.

The last clinical assessment, carried out 8 months after the first consultation, showed a weight loss of 44 kg, with a BMI of 53.62 kg/m². Laboratory tests showed an Ht of 61%, maintaining the indication for periodic therapeutic phlebotomy, while the other parameters showed no relevant changes. Clinically, there was a significant improvement in daytime sleepiness, and polysomnography was requested for further assessment, but not yet carried out. The therapeutic regimen was maintained with adjustments, replacing semaglutide with tirzepatide 10 mg/week, prednisone 5 mg/day and 350 mL bloodletting. The major therapeutic challenge in this case is to control the CAH and the progression of TART, in order to prevent it from evolving into Cushing's syndrome, as well as adjusting weight and managing associated comorbidities.

DISCUSSION

Congenital adrenal hyperplasia (CAH) is a heterogeneous group of diseases that compromise the synthesis of adrenocortical steroids. Among its variants, the form resulting from 11β-hydroxylase deficiency is rare, with a prevalence of approximately 1:100,000 live births, predominating in North African and Middle Eastern populations, while 21- hydroxylase deficiency is more frequent and occurs mainly in Eastern Europe and among Jews (10). 11β-hydroxylase deficiency stands out for its association with hypertension, polyglobulia and the accumulation of hormone precursors such as 11-deoxycorticosterone (DOCA) (10,11).

In the case reported, although the initial diagnosis pointed to the classic form due to 21-hydroxylase deficiency, the presence of chronic hypertension associated with markedly elevated levels of DOCA and the occurrence of refractory polyglobulia strongly suggest the possibility of an 11β-hydroxylase deficit. The family history reinforces this suspicion, as the patient's sister had typical female manifestations, such as ambiguous genitalia and dehydration, highlighting the hereditary nature and severity of the condition.

Since childhood, the patient has shown classic signs of hyperandrogenism, including precocious puberty at eight months, with pubic hair and testicular enlargement, compatible with ACTH hyperstimulation due to cortisol deficiency. The development of severe obesity also fits into the context of hormonal dysfunctions typical of CAH. Although treatment with glucocorticoids is essential, its adverse effects, such as increased BMI and higher blood pressure, are well documented (10). In the present case, prolonged periods of interruption in follow-up and iatrogenic use of high doses of glucocorticoids contributed to chronic complications, including excessive weight gain, systemic arterial hypertension and the development of testicular adrenal rest tumors (TARTs).

TARTs are common benign tumors in men with CAH, even under appropriate treatment (3). They are usually bilateral and close to the testicular mediastinum (6, 8), and can cause obstruction of the seminiferous tubules, azoospermia and irreversible local damage (7). Usually diagnosed after the age of 10, their growth is stimulated by pubertal hormones, with ACTH being the main tumor inducer (8). Differential diagnosis with Leydig cell tumors (LCTs) is

essential, since TARTs are bilateral in around 80% of cases, while Leydig tumors are mostly unilateral (around 97%) (2). Early treatment can reduce tumor volume, although its effectiveness is not fully established (7), and surgery is usually reserved for cases with significant pain or discomfort (8). Testicular Doppler ultrasound is the imaging method of choice, identifying hypoechogenic and vascularized masses (1). Despite their potential impact, TARTs can be asymptomatic (4).

Another relevant point in the case is the presence of severe polyglobulia that is refractory to clinical treatment, with a hematocrit frequently above 60%. This finding is more characteristic of 11β-hydroxylase deficiency than of the classic form due to 21- hydroxylase deficiency, and seems to be related to both the excess of androgens and the action of DOCA on erythropoiesis. The introduction of therapeutic phlebotomy provided partial relief of symptoms, although without normalizing the hematimetric parameters. Severe obesity, with a BMI of over 60 kg/m², was a major aggravating factor. The introduction of treatment resulted in significant weight loss within a few months, promoting significant functional improvement and potentially having a positive impact on obstructive sleep apnea and hypertension control.

Irregular adherence to treatment contributed significantly to the worsening of the clinical condition, highlighting the importance of strict hormonal monitoring, continuous health education and multidisciplinary follow-up. These aspects are fundamental to preventing complications of CAH, reinforcing the importance of early diagnosis and intervention. The case illustrates the complexity of managing classic CAH, especially when associated with less

prevalent forms, such as 11β-hydroxylase deficiency. The integration of early diagnosis, appropriate therapy, ongoing screening for complications and patient adherence to treatment is essential to minimize long-term morbidities, including infertility, testicular dysfunction, cardiovascular complications and metabolic disorders.

CONCLUSION

This clinical case highlights the complexity of Congenital Adrenal Hyperplasia (CAH) and its potential long-term systemic complications, particularly the development of residual testicular adrenal tumors (TARTs). The history of chronic hormonal dyscontrol, demonstrated by persistently high levels of 17-hydroxyprogesterone (17-OHP) and ACTH, not only favored the formation and progression of TARTs, but also contributed to an aggravated metabolic condition, marked by severe obesity and systemic hypertension.

The management of these patients requires a multidisciplinary approach, with close monitoring and consistent adherence to glucocorticoid therapy, with the aim of adequately suppressing ACTH and possibly containing tumor growth. Serial testicular ultrasound stands out as an essential tool for early screening, follow-up and differentiation between TARTs and other testicular masses. Male infertility, mainly due to compression of the seminiferous tubules by the tumors, is one of the most serious complications, with a risk of irreversible testicular damage, since even testicular preservation surgery does not guarantee recovery of reproductive function.

In short, this case reinforces the importance of early diagnosis of CAH, adherence to hormone treatment and continuous clinical follow-up to control complications. Patient education and awareness of the long-term risks, especially infertility, are essential to enable shared decisions, timely interventions and, consequently, a better quality of life and prognosis.

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