AACE Clinical Case Rep. 7 (2021) 342–345

Contents lists available at ScienceDirect

AACE Clinical Case Reports

journal homepage: www.aaceclinicalcasereports.com

Case Report

A Gigantic Uterine Leiomyoma and Big Bilateral Adrenal Myelolipomas as a Result of Untreated Congenital Adrenal Hyperplasia

Betty La, MD [1,*], Celestine Tung, MD [2], Eugene A. Choi, MD [3], Ha Nguyen, MD [1]

[1] Section of Endocrinology, Diabetes and Metabolism, Baylor College of Medicine, Houston, Texas
[2] Division of Gynecologic Oncology, Baylor College of Medicine, Houston, Texas
[3] Division of Surgical Oncology, Baylor College of Medicine, Houston, Texas

ARTICLE INFO

Article history:
Received 12 March 2021
Received in revised form
30 April 2021
Accepted 5 May 2021
Available online 13 May 2021

Key Words:
adrenal myelolipoma
congenital adrenal hyperplasia
uterine leiomyoma

ABSTRACT

Introduction: Patients with congenital adrenal hyperplasia (CAH) can present early with salt wasting, adrenal insufficiency, and hyperandrogenism. Late consequences as a result of untreated CAH are now rarely seen. We present a patient with a massive uterine leiomyoma and bilateral adrenal myelolipomas due to longstanding treatment noncompliance.
Case Report: A female patient with CAH was treated with glucocorticoids until the age of 29 years when they stopped with the intention of identifying as a male. The patient then presented with abdominal pain and distension. Computed tomography images of the abdomen and pelvis revealed a 31 × 35 × 31-cm abdominal mass, a 5.9× 2.4-cm right adrenal mass, and an 11.8 × 8.8-cm left adrenal mass. The patient underwent total hysterectomy and bilateral adrenalectomy. Pathology of the abdominal mass was consistent with uterine leiomyoma, and bilateral adrenal masses were consistent with adrenal myelolipomas.
Discussion: The goal of CAH therapy is to provide adequate replacement while reducing adrenocorticotropic hormone and adrenal androgens levels. Due to the conversion of androgens to estrogens, untreated females with CAH have elevated androgen and estrogen levels. High levels of these hormones can stimulate the growth of estrogen-dependent organs as exemplified by our patient. Chronic adrenocorticotropic hormone stimulation can not only cause adrenal hyperplasia but has also been associated with the development of adrenal myelolipomas.
Conclusion: This case demonstrates the significance of CAH treatment compliance as there are several serious sequela outside of the expected adrenal insufficiency and virilization. Even when the desired effect is virilization, other means of hormonal therapy should be considered.

Introduction

Congenital adrenal hyperplasia (CAH) is a rare group of inherited autosomal recessive disorders characterized by a deficiency in glucocorticoids and mineralocorticoids.[1] The most common form is caused by 21-hydroxylase deficiency in 95% of cases. CAH can be further subdivided into salt wasting, simple virilizing, and nonclassical forms. Salt wasting CAH, the most severe form, typically presents early with hypovolemia, adrenal insufficiency, and hyperandrogenism. Simple virilizing CAH is less severe as patients produce sufficient mineralocorticoids, but they can still have severe hyperandrogenism. Nonclassical CAH is the mildest form with varying presentations from asymptomatic to mild hyperandrogenism.[2]

With the inclusion of CAH in newborn screenings, most classical cases are diagnosed and treated early in life.[3] However, finding the right balance in treatment can be challenging because both overtreatment and undertreatment have inherent risks. Overtreatment with glucocorticoids can lead to obesity, bone loss, and other metabolic complications. Inadequate treatment can cause adrenal insufficiency, complications related to infertility, and adrenal rest tumors.[1] Less commonly, chronically untreated patients can develop unusual complications, including uterine leiomyomas and adrenal myelolipomas.[2,4]

Abbreviations: ACTH, adrenocorticotropic hormone; CAH, congenital adrenal hyperplasia; 17-OHP, 17-hydroxyprogesterone.

* Address correspondence and reprint requests to Dr Betty La, Section of Endocrinology, Diabetes and Metabolism, Baylor College of Medicine, 7200 Cambridge St., Houston, TX 77030.
E-mail address: Betty.La@BCM.edu (B. La).

https://doi.org/10.1016/j.aace.2021.05.002

We present a rare case of uterine leiomyoma and bilateral adrenal myelolipomas in a patient with CAH due to longstanding treatment noncompliance.

Case Report

The patient was born as a female with ambiguous genitalia and diagnosed with CAH shortly after birth. The specific enzyme deficiency is unknown, and no records were available for review. The patient was started on glucocorticoid replacement and raised as a female. At the age of 29 years, the patient stopped glucocorticoids on their own, with the intention of identifying as a male. The patient gradually developed desired male features, including deepening voice and hirsutism. Menstrual cycles became irregular and eventually stopped altogether. During this time off glucocorticoids, no symptoms of adrenal insufficiency or crisis episodes were noted.

At the age of 37 years, the patient presented with abdominal distension, vomiting, and hypotension. The result of physical examination was consistent with untreated CAH with hirsutism and clitoromegaly and was notable for significant abdominal distension. Serum biochemical measurements demonstrated sodium, cortisol, adrenocorticotropic hormone (ACTH), 17-hydroxyprogesterone (17-OHP), androstenedione, total testosterone, and estradiol levels of 126 meq/L (136-145), 78.5 μg/dL (3.7-19.4), 166 pg/mL (6-50), 4356 ng/dL (≤285), 7188 ng/dL (35-250), 737 ng/dL (2-45), and 142 pg/mL (48-440), respectively (Table). Of note, the laboratory specimens were collected after the initial dose of hydrocortisone was administered for adrenal crisis. The patient denied exogenous testosterone treatment. Computed tomography images of the abdomen showed a right adrenal mass (5.9 × 2.4 cm) and a left adrenal mass (11.8 × 8.8 cm). Furthermore, the images revealed a large abdominal mass (31 × 35 × 31 cm) that displaced nearly all intra-abdominal contents posteriorly. The mass was hypervascular, with areas of hypoattenuation and internal necrosis (Fig. 1). Biochemical work-up of the adrenal masses was unremarkable with aldosterone, renin, plasma free metanephrine, and plasma free normetanephrine levels of <1 ng/dL (3-16), 0.45 ng/mL/h (0.25-5.82), 56 pg/mL (≤205), and 56 pg/mL (≤148), respectively (Table).

The consensus of a multidisciplinary discussion between endocrinology, surgical, and gynecologic oncology was for the resection of the pelvic and adrenal masses. As the surgical plan included a bilateral oophorectomy, fertility preservation was discussed with the patient. The patient had no interest in preserving ovarian function and underwent an uncomplicated hysterectomy with bilateral salpingo-oophorectomy and bilateral adrenalectomy (Fig. 2). Abdominal mass pathology revealed a uterine leiomyoma, whereas the adrenal mass pathology demonstrated bilateral adrenal myelolipomas in a background of diffuse macronodular and micronodular hyperplasia with scattered lymphocytic aggregates and areas of hemorrhage. Postoperatively, the patient was started on stress dose hydrocortisone, which was tapered to physiologic doses, and fludrocortisone was subsequently added. At a follow-up visit 4 weeks later, total testosterone levels decreased to <12 ng/dL. At 12 weeks after surgery, the patient was started on transdermal testosterone with satisfactory results.

Table
Laboratory Test Results

Test	Laboratory result	Reference range
Sodium (meq/L)	126	136-145
Cortisol[a] (μg/dL)	78.5	3.7-19.4
Adrenocorticotropin hormone (pg/mL)	166	6-50
17-hydroxyprogesterone (ng/dL)	4356	≤285
Total testosterone (ng/dL)	737	2-45
Androstenedione (ng/dL)	7188	35-250
Estradiol (pg/mL)	142	48-440
Aldosterone (ng/dL)	<1	3-16
Renin (ng/mL/h)	0.45	0.25-5.82
Plasma metanephrines (pg/mL)	56	≤205
Plasma normetanephrines (pg/mL)	45	≤148

[a] Cortisol was collected after the administration of hydrocortisone treatment for adrenal crisis.

Discussion

Glucocorticoids and mineralocorticoids are the mainstays of CAH treatment, with the goal of providing adequate replacement while reducing ACTH and adrenal androgens. Patients are clinically monitored to determine sufficient dosing, and 17-OHP and androstenedione levels can be used as markers to help assess treatment adequacy. Although not recommended for routine monitoring, elevated ACTH levels can indicate uncontrolled CAH.[1] Our patient presented with high ACTH and 17-OHP levels, consistent with medication noncompliance. The patient was off therapy for several years without symptoms or episodes of adrenal crises until they developed a significant physical stress from the abdominal and adrenal masses. It is unclear why several patients with CAH can survive for several years without glucocorticoids, although it is possibly related to the accumulation of high levels of 17-OHP, which has been suggested to act as a partial glucocorticoid agonist.[5]

A persistently elevated ACTH in undertreated or untreated CAH not only causes adrenal hyperplasia but is also associated with the development of other adrenal masses.[6] Previous studies have reported the prevalence of adrenal masses in CAH to be between 11% and 83%, whereas Nermoen et al[4] estimated the prevalence to be 29.3%.[7] Given the rarity of this disease, the exact prevalence of adrenal masses in CAH remains unclear, but it seems to be higher than that reported in the general population (3% in middle ages and up to 15% in the older adults).[8]

Adrenal myelolipomas are tumors composed of fat interspersed with hematopoietic elements resembling the bone marrow.[9] The occurrence of myelolipomas appears to be higher in CAH than that in the general population. Nermoen et al[4] found the prevalence of myelolipomas in CAH to be 7.4%, whereas its prevalence in the general population was found to be 0.37%-1.5%.[10] Most myelolipomas are small (<4 cm) and unilateral, with a predominance for a left-sided disease. This is believed to be due to unrestricted growth without the confining presence of the liver.[11] Consistent with this theory, our patient's left myelolipoma was larger (17 cm) than the right myelolipoma (8 cm). Bilateral adrenal myelolipomas are uncommon but have been reported with increasing frequency. In a recent meta-analysis, up to 59.6% of patients with CAH with adrenal myelolipomas were found to have a bilateral disease.[4] Their etiology is unknown; however, it has been speculated that chronic ACTH stimulation may play a role in myelolipoma development. Although benign, myelolipomas can become hormonally functional or cause mass effect, hemorrhage, and become necrotic when reaching a large enough size.[9,12] Several factors influence the management decisions of myelolipomas; however, typically, myelolipomas that are symptomatic and >7 cm in size are recommended for surgical excision.[13,14] Evidence indicates that bilateral adrenalectomy is a reasonable therapeutic option with low rates of morbidity and mortality. Most patients with CAH who underwent bilateral adrenalectomy reported improvement in hyperandrogenic symptoms, with a significant reduction in glucocorticoid doses. Adrenal crises were the most common complication of bilateral adrenalectomy (17%) followed by adrenal rest tumors (10%), underlining the significance of continued follow-up.[14] Given that myelolipomas do occur with increased frequency in patients with CAH, they should

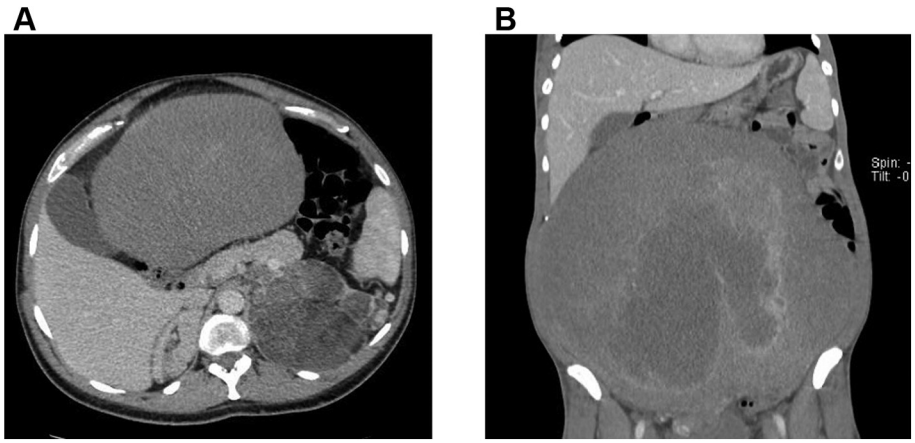

Fig. 1. Computed tomography images demonstrating a right adrenal mass (5.9 × 2.4 cm), left adrenal mass (11.8 × 8.8 cm), and large abdominal mass (31 × 35 × 31 cm). *A*, Axial view of the right adrenal mass, left adrenal mass, and abdominal mass. *B*, Coronal view of the abdominal mass. The abdominal mass displaces the entire abdomen and nearly all intra-abdominal contents posteriorly. The mass is hypervascular with areas of hypoattenuation and possible internal necrosis.

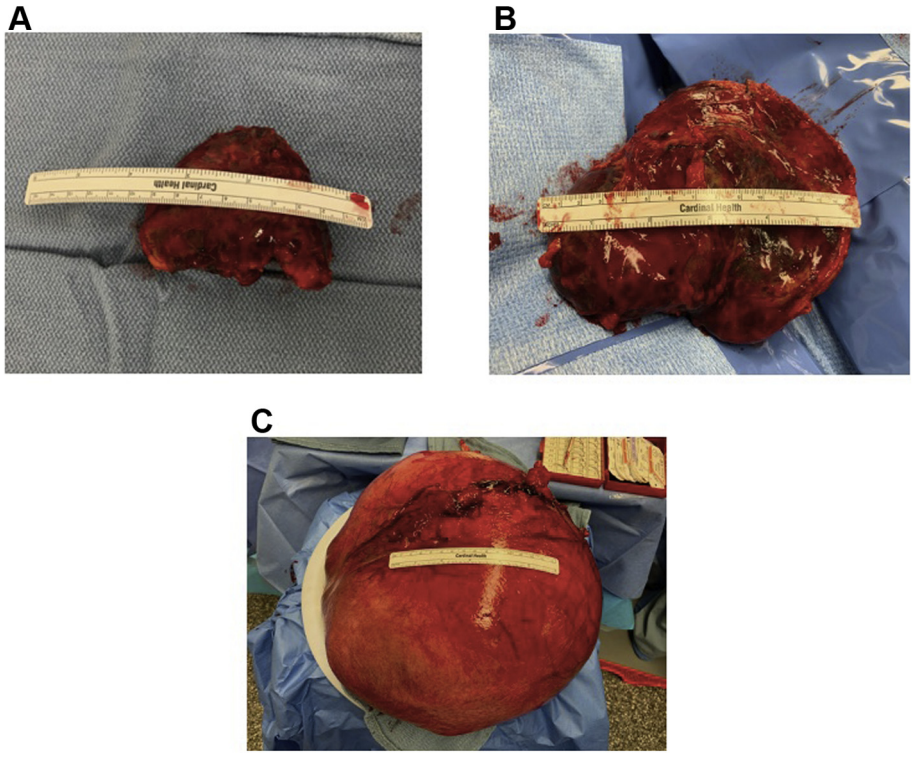

Fig. 2. Gross surgical pathology of: *A*, right adrenal mass (8 × 4.6 × 3.2 cm); *B*, left adrenal mass (17 × 14 × 4.2 cm); and *C*, abdominal mass (38 × 32 × 30 cm).

be considered in the differential diagnosis in patients with CAH with abdominal pain, nausea, and vomiting, especially if there is a known medication noncompliance. There are no current guidelines for the screening of patients with CAH for these complications, but perhaps should be considered. The early diagnosis of myelolipomas may allow for early intervention to prevent the complications that our patient experienced.

High levels of adrenal androgens can cause several unwanted gynecologic complications in a patient with uncontrolled CAH.[1] Due to the conversion of androgens to estrogens, untreated females with CAH have significantly elevated levels of both hormones. In addition, high androgen and estrogen levels stimulate the growth of estrogen-dependent organs, leading to the development and growth of uterine leiomyomas. A high estrogen level has been linked to the development of leiomyomas; however, data regarding how both estrogen and testosterone affect the uterus have been conflicting and limited. Previous studies have found that testosterone did not stimulate uterine proliferation and may even suppress it in vitro.[15,16] A study by Wong et al[17] evaluated the effects of both hormones on leiomyoma development and found that women with elevated testosterone levels were at a higher risk of developing uterine leiomyomas. Furthermore, women with both elevated testosterone and estrogen levels had an even higher risk of leiomyoma development than those with an elevated testosterone level alone. Our patient did not have an elevated estradiol but had elevated testosterone and androstenedione levels, which likely led to uterine proliferation and a large leiomyoma. There are no known studies to date that evaluate the prevalence of uterine leiomyomas

in CAH. In our literature search, there were only 3 previously reported cases of large uterine leiomyomas in patients with CAH.[18–20] It is unclear if uterine leiomyomas are as uncommon as suggested by the literature search or if their prevalence in this population is higher but not reported as much because they may be a common occurrence in the general population. To our knowledge, this is the first case of a patient with CAH with a fibroid of this significant size reported in the literature.

Conclusion

This case demonstrates the significance of CAH treatment compliance, since there are several serious sequela outside of the expected adrenal insufficiency and virilization. Even when the desired effect is virilization, other means of hormonal therapy should be considered due to risks of abnormal growth of certain organs sensitive to excess androgens, estrogens, and ACTH.

Acknowledgment

This case report was first published as an abstract at the Endocrine Society Online annual meeting March 28-31, 2020.

Disclosure

The authors have no multiplicity of interest to disclose.

References

1. Speiser PW, Arlt W, Auchus RJ, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2018;103(11):4043–4088.
2. White PC, Speiser PW. Congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Endocr Rev*. 2000;21(3):245–291.
3. Brosnan PG, Brosnan CA, Kemp SF, et al. Effect of newborn screening for congenital adrenal hyperplasia. *Arch Pediatr Adolesc Med*. 1999;153(12):1272–1278.
4. Nermoen I, Falhammar H. Prevalence and characteristics of adrenal tumors and myelolipomas in congenital adrenal hyperplasia: a systematic review and meta-analysis. *Endocr Pract*. 2020;26(11):1351–1365.
5. Pijnenburg-Kleizen KJ, Engels M, Mooij CF, et al. Adrenal steroid metabolites accumulating in congenital adrenal hyperplasia lead to transactivation of the glucocorticoid receptor. *Endocrinology*. 2015;156(10):3504–3510.
6. Bachelot A, Chakthoura Z, Rouxel A, Dulon J, Touraine P. Classical forms of congenital adrenal hyperplasia due to 21-hydroxylase deficiency in adults. *Horm Res*. 2008;69(4):203–211.
7. Jaresch S, Kornely E, Kley H, Schlaghecke R. Adrenal incidentaloma and patients with homozygous or heterozygous congenital adrenal hyperplasia. *J Clin Endocrinol Metab*. 1992;74(3):685–689.
8. Arnaldi G, Boscaro M. Adrenal incidentaloma. *Best Pract Res Clin Endocrinol Metab*. 2012;26(4):405–419.
9. Decmann Á, Perge P, Tóth M, Igaz P. Adrenal myelolipoma: a comprehensive review. *Endocrine*. 2018;59(1):7–15.
10. Lezoche E, Guerrieri M, Crosta F, et al. Perioperative results of 214 laparoscopic adrenalectomies by anterior transperitoneal approach. *Surg Endosc*. 2008;22(2):522–526.
11. Ferreira F, Martins JM, do Vale S, Esteves R, Nunes G, Carmo Id. Rare and severe complications of congenital adrenal hyperplasia due to 21-hydroxylase deficiency: a case report. *J Med Case Rep*. 2013;7:39.
12. Sherlock M, Scarsbrook A, Abbas A, et al. Adrenal incidentaloma. *Endocr Rev*. 2020;41(6):775–820.
13. Daneshmand S, Quek ML. Adrenal myelolipoma: diagnosis and management. *Urol J*. 2006;3(2):71–74. Accessed July 20, 2020.
14. MacKay D, Nordenström A, Falhammar H. Bilateral adrenalectomy in congenital adrenal hyperplasia: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2018;103(5):1767–1778.
15. Zang H, Sahlin L, Masironi B, Eriksson E, Lindén Hirschberg A. Effects of testosterone treatment on endometrial proliferation in postmenopausal women. *J Clin Endocrinol Metab*. 2007;92(6):2169–2175.
16. Rose GL, Dowsett M, Mudge JE, White JO, Jeffcoate SL. The inhibitory effects of danazol, danazol metabolites, gestrinone, and testosterone on the growth of human endometrial cells in vitro. *Fertil Steril*. 1988;49(2):224–228.
17. Wong JYY, Gold EB, Johnson WO, Lee JS. Circulating sex hormones and risk of uterine fibroids: study of women's health across the nation (SWAN). *J Clin Endocrinol Metab*. 2016;101(1):123–130.
18. Fujita S, Kushihata F, Yachnis A, Winter W, Schell S. Images of interest. Gastrointestinal: symptomatic pelvic mass. *J Gastroenterol Hepatol*. 2004;19(7),826-826.
19. Brown WW, Toyama P, Gonzales W. Multiple uterine leiomyomas developed in the presence of a high androgen environment secondary to adrenogenital syndrome. *Obstet Gynecol*. 1970;35(2):255–259.
20. Sege D, Siebenmann RE. Giant uterine myoma in a congenital adrenogenital syndrome. *Schweiz Med Wochenschr*. 1973;103(49):1743–1749.