

# BILATERAL OVARY ADRENAL REST TUMOR IN A CONGENITAL ADRENAL HYPERPLASIA FOLLOWING ADRENALECTOMY

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## ABSTRACT

**Objective:** In contrast to the high incidence of testicular adrenal rest tumors in adult male patients with congenital adrenal hyperplasia (CAH), ovarian adrenal rest tumors (OARTs) in female CAH patients are rare. In this case report, we describe a case of bilateral OART in a female patient with CAH due to 21-hydroxylase deficiency.

**Methods:** We present a detailed case report with the clinical, imaging, and laboratory findings of the patient. The pertinent literature is also reviewed.

**Results:** A 17-year-old patient was known to have CAH due to 21-hydroxylase deficiency. Since the second month of her gestational age, her mother was treated with cortisone-replacement therapy. The patient was treated with hydrocortisone and fludrocortisone since the neonatal period. Her pertinent history included a bilateral adrenalectomy at the age of 13 years in 2006, and for 3 years she led a normal puberty life with no complaint with hormonal replacement therapy. Nevertheless, in 2009, she developed a virilizing syndrome. Subsequently, she underwent surgery in December 2009 for right adnexectomy. However, the regression of the masculinizing mass was not complete and worsened several months after the surgery. A new pelvic magnetic resonance image showed the activation of a

contralateral ovarian mass, necessitating a left adnexectomy in August 2010.

**Conclusion:** This case demonstrates some interesting features of OART that pose challenges to its management. If an OART is detected early enough and glucocorticoid therapy is received, it is possible that the OART will decrease in size following suppression of adrenocorticotrophic hormone levels. (*Endocr Pract.* 2014;20:e69-e74)

## Abbreviations:

**ACTH** = adrenocorticotrophic hormone; **ART** = adrenal rest tumor; **CAH** = congenital adrenal hyperplasia; **CYP21A2** = congenital hyperplasia gene; **MRI** = magnetic resonance imaging; **OART** = ovarian adrenal rest tumor

## INTRODUCTION

Congenital adrenal hyperplasia (CAH) describes a group of autosomal recessive disorders resulting in the deficiency of one of the enzymes required to synthesize cortisol (1). CAH is primarily caused by mutations in the steroid 21-hydroxylase gene (*CYP21A2*) (2). 21-Hydroxylase deficiency accounts for 90 to 95% of cases of CAH (1). A result of this deficiency is increased production of corticotropin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH) by the pituitary gland. The clinical consequences are hypertrophy of the adrenal glands and the accumulation of precursor hormones with overproduction of adrenal androgens (3,4). These precursors are shunted into the androgen biosynthesis pathway, producing virilization in the female fetus or infant and rapid postnatal growth with accelerated skeletal maturation, precocious puberty, and short adult stature in both males and females. Females with classic CAH present at birth with ambiguous genitalia, whereas males do not have abnormalities at birth (5).

Adrenal rest tumors (ARTs) are extra-adrenal manifestations of adrenal tissue, and 50% of neonates with CAH

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have an ART. ARTs gradually undergo involution, with the subsequent prevalence falling to 1% by adulthood (6). For men with CAH, testicular adrenal rest tumors (TARTs) are common, with a prevalence as high as 95% in some reports, and detection can occur as early as childhood (7). A TART is a benign tumor that most often presents bilaterally and is located in the rete testis (3). Ovarian adrenal rest tumors (OARTs) are another, albeit less common, form of an extra-adrenal tissue that can occur in females with CAH (8). Other locations of ARTs, such as in the perirenal region in a patient with CAH due to congenital 3-beta-hydroxysteroid dehydrogenase (HSD3B2) deficiency in the Netherlands in 2008, have seldom been reported (9).

To date, only 11 cases of OART have been described in the English-language literature (10,11), making it difficult to choose an optimal treatment approach for affected patients. Here, we add the case of a 17-year-old girl with CAH who underwent bilateral adrenalectomy at the age of 13 years and later developed bilateral OART (Table 1).

## CASE REPORT

The young female patient was known to have classic CAH due to 21-hydroxylase deficiency or *CYP21A2* mutation. Her family history was contributory for CAH. She has 22- and 26-year-old elder sisters who have severe CAH and normal 6- and 10-year-old brothers. She also had a sister affected with hydramnios who died in utero in the fourth month of gestation and a brother who died at the age of 10 days in 1983 as a consequence of undertreatment of the salt-losing form of CAH.

Treatment of the patient began in utero; her mother was treated with dexamethasone beginning in the second month of gestation. After her birth, the newborn patient was given fludrocortisone acetate and hydrocortisone replacement therapy. Her karyotype at birth was 46,XX. In 1995, at the age of 6 months, she underwent surgery for minor ambiguous genitalia.

Therapy for *CYP21A2* deficiency is directed toward providing glucocorticoid in sufficient doses to reduce the

degree of hyperandrogenemia, so that growth, sexual maturation, and later, reproductive function, are normal. In this young patient, these goals were difficult to achieve without overtreatment and its attendant risk of clinical manifestations of Cushing's syndrome. In fact, the patient had primary amenorrhea and failed to develop female secondary sexual characters by the age of 13 years. Subsequently, in order to prevent hyperandrogenism signs and cushingoid appearance, she underwent a bilateral adrenalectomy in June 2006. The surgery resulted in a 23-gram right and a 31-gram left adrenal gland, with diffuse hyperplasia and a predominant reticular layer, as reported by the pathologist (Fig. 1).

After the bilateral adrenalectomy, the patient had menarche with regular menstrual cycles, and she grew to reach her definite height of 165 cm, which was 10-cm taller than her two elder sisters. She was single and had never been pregnant. In addition, reversal of the patient's virilization and increased estrogenization has become noticeable as acne and hirsutism. In addition, her rasping voice regressed, and she developed female secondary sexual characteristics. However, the patient was increasingly hyperpigmented. Endocrinologic laboratory studies showed delta-4 androstenedione levels of 27 and 0.03 ng/mL 1 day pre- and 4 days postbilateral adrenalectomy, respectively (normal values, 0.2 and 3.1 ng/mL, respectively). Follicle-stimulating hormone, luteinizing hormone, and estradiol levels were in the normal range (Table 1).

The clinical presentation remained uneventful for 3 years, until a secondary amenorrhea occurred. The patient also noticed alteration in her voice's pitch again, a reappearance of acne, hirsutism, and coarse, dark hair, predominantly on her face. An evaluation of her hormonal status revealed an elevated testosterone level of 675 ng/dL (normal range, 0 to 81 ng/dL) as well as increases in the levels of 17-hydroxyprogesterone and delta-4-androstenedione to 29.6 ng/dL and 9.97 ng/mL, respectively (Table 1). Pelvic magnetic resonance imaging (MRI) showed a 3-cm hyperinjected right ovary tumor with normal contralateral ovary (Fig. 2 A). Right salpingo-oophorectomy was

**Table 1**  
**Hormonal Data**

|                                            | 02/06/2006 | 06/06/2006                  | 10/10/2009                            | 19/05/2010                           | 16/08/2010                         | 01/2011                             |
|--------------------------------------------|------------|-----------------------------|---------------------------------------|--------------------------------------|------------------------------------|-------------------------------------|
|                                            |            | adrenalectomy<br>02/06/2006 | Pre left<br>annexectomy<br>28/12/2009 | Post right<br>annexectomy<br>05/2010 | Pre left<br>annexectomy<br>08/2010 | Post left<br>annexectomy<br>01/2011 |
| 17-OH<br>progesterone ng/ml [0.2-2.6]      |            | 2.56                        | 29.6                                  | 7.32                                 | 4.49                               | 1.57                                |
| Delta 4 androstenedione<br>ng/ml [0.2-3.1] | 27         | 0.03                        | 9.97                                  | 2.91                                 | 2.79                               | 0.17                                |
| Testosterone mg/dl [0-81]                  | 576        |                             | 675                                   | 461                                  | 557                                |                                     |

then performed by coeloscopy in December 2009 (Fig. 3). Gross examination of the specimen disclosed a 3-cm, well-delineated, brownish mass of the ovary. Microscopically, the tumor was composed of large cells with abundant eosinophilic cytoplasm and regular nuclei. The tumor cells displayed a seroid histologic and immunohistochemical phenotype similar to the one observed in the previously resected adrenal glands.

Immunostaining demonstrated expression of vimentin and Mart-1 by both the ovarian tumor and hyperplastic adrenal gland cells and focal expression of calretinin, inhibin, and progesterone receptors. The immunoprofile was specific for adrenal cortical tissue. Estrogen receptors, HMB45, S100 protein, chromogranin A, and CD100 were negative, excluding other differential diagnoses such as a malignant melanoma, neuroendocrine tumor, or metastatic renal cell carcinoma. After discussions, we rejected the hypothesis of a primary ovarian steroid cell tumor and retained the diagnosis of hyperplastic adrenal remnant of the right ovary.

However, the clinical picture did not improve as much as expected, as the patient noted just a transitory improvement. Indeed, a recurrence of defeminization manifested several months after the right adnexectomy was performed. Hormonal follow-ups in May 2010 and August 2010 revealed that the rise in hormone levels was not as high as at the time of the right ovary mass in 2009. The levels of 17-hydroxyprogesterone in May and August 2010 were 7.32 and 4.49 ng/mL, respectively, whereas the May and August 2010 levels of delta-4-androstenedione were 2.91 and 2.79 ng/mL and those of testosterone were 461 and 557 mg/dL, respectively (Table 1).

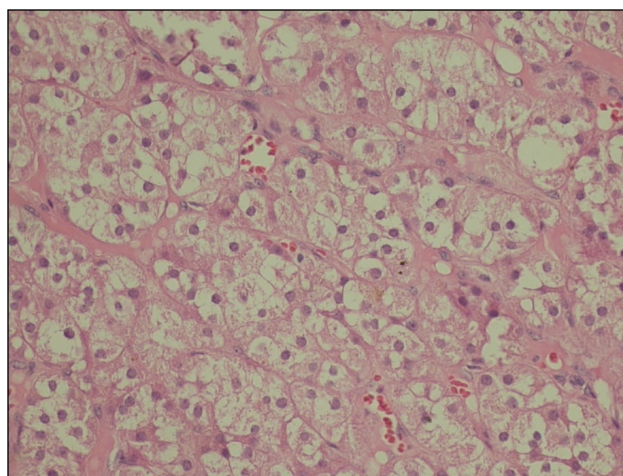


**Fig. 1.** Microscopic appearance of adrenal gland hyperplasia (H&E stain,  $\times 200$ ). H&E = hematoxylin and eosin.

Given these circumstances, a pelvic MRI was repeated and showed a left ovary mass tumor, which explained the new onset of virilizing syndrome (Fig. 2 B). The patient subsequently underwent a contralateral adnexectomy in August 2010. The left ovarian mass was histologically similar to the right ovarian mass.

## DISCUSSION

OART is a rare manifestation of CAH due to 21-hydroxylase deficiency in female patients, with the first case reported in the literature in 1957 (12). A systematic review of the English-language literature by Tiosano et al



**Fig. 2.** Magnetic resonance imaging (MRI) of the pelvis. A) MRI of the pelvis performed on December 28, 2009, which disclosed a  $35 \times 25$  mm right ovarian mass that showed at the arterial phase of the dynamic sequence a homogeneous high-contrast uptake (arrow) typical of endocrine tissue. B) Repeated MRI at the arterial phase shows a  $17 \times 13$  mm ovarian mass situated in the left ovary (arrow) between the uterus and the left external iliac vessels. It had the same characteristics of the previously removed right ovarian mass. At higher levels (not shown), other similar lesions were detected that proved to be located in the left lumbo-ovarian ligament at laparotomy.

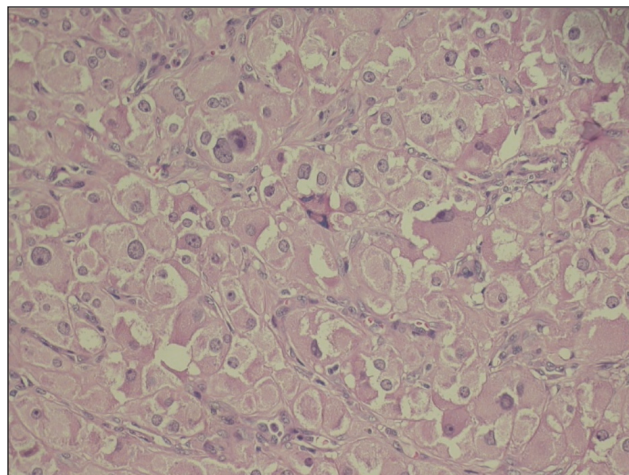


**Fig. 3.** Microscopic appearance of the right ovary mass (H&E  $\times 200$ ). Steroid cell tumor is similar to the adrenal gland hyperplasia. H&E = hematoxylin and eosin.

(10) in 2010 revealed only 10 confirmed cases (10). Our own search revealed an additional case report published in 2003 in Nigeria (11), which was not mentioned by Tiosano et al. These patients ranged in age from 2 to 41 years, and all exhibited elevated ACTH levels (Table 2).

Of the 11 cases in the literature, 9 cases involved CAH, and 3 of these cases were due to undefined enzyme deficiency, 3 were due to 21-hydroxylase deficiency (including the current case), 2 were due to 11-hydroxylase deficiency, and 1 was due to HSD3B2 deficiency. Three cases involved patients with Cushing's disease who underwent bilateral adrenalectomy, two of whom developed Nelson's syndrome following the adrenalectomy.

The rapidity of evolution is a particular feature of the present case that is not found elsewhere in the literature. The rapidity of development of the contralateral ovary mass, which would lead to a high suspicion of ovarian cancer, is in contrast to the unilateral or concomitant bilateral ovary tumors reported in other cases.

For the clinician, the severity of the OART must not be underestimated, as misdiagnosis can be fatal for the patient (8). However, prompt diagnosis of OART can be elusive. This raises a concern regarding the lack of defined criteria for a radiologic diagnosis of OART (13). Routine ovarian imaging in CAH females is not indicated. However, when ovarian dysfunction is present, ovarian imaging is advised, first by ultrasonography, to detect OARTs or polycystic ovaries.

A study conducted in the United States in 2012 showed that  $^{18}\text{F}$ -labeled fluoro-2-deoxy-d-glucose positron

emission tomography/computed tomography scanning with cosytropin stimulation can accurately identify adrenal rest tissue not visualized with conventional imaging in CAH patients after an adrenalectomy, thus allowing for successful surgical resection (14).

Although ARTs of the ovary are generally associated with some features of masculinization, it would be reasonable to suggest that the clinical picture is mostly influenced by zonal predominance of the mass. The virilizing picture suggests the involvement of the reticularis zona and its predominance (11).

Nelson's syndrome occurs in 10 to 35% of patients treated for Cushing's disease by bilateral adrenalectomy (15). Cortisol-producing testicular tumors activated by markedly elevated ACTH levels have been described in male patients with Nelson's syndrome. In 1982, Verdonk et al (15) described the case of a female patient who presented with activation of virilizing adrenal rest tissues by excessive ACTH production. This was due to Nelson's syndrome postadrenalectomy for Cushing's disease. In our case, a cerebral MRI was performed in order to eliminate the possibility of Nelson's syndrome; nonetheless, the results showed a pituitary gland in the upper limit of normal, without evidence of an adenoma.

The optimal treatment of the ovaries in cases of OART remains unclear, as multiple approaches have been utilized. In our case, given the results of MRI, a surgical approach of bilateral adrenalectomy, right salpingo-oophorectomy, and bilateral adnexectomy were elected. Although unfamiliarity with the diagnosis of OART may lead to unnecessary surgical treatment, the large size of the tumor coupled with lack of outcome data may justify removal in some instances.

## CONCLUSION

In conclusion, whether surgical treatment for ART is advised remains unclear due to the rarity of these tumors. For girls and women with CAH for whom medical treatment is unavailable or who are noncompliant with their therapy, OART should be considered when ovarian masses are detected. If an OART is detected early enough and glucocorticoid therapy is received, it is possible that the OART will decrease in size following suppression of ACTH levels.

## DISCLOSURE

The authors have no multiplicity of interest to disclose.

**Table 2**  
**Cases of Ovarian Adrenal Rest Tumors**

| Diagnosis               | Age and symptoms at OART diagnosis / Treatment Plan                                                                                                                  | Adrenalectomy | Virilization              | Bilateral ovarian adrenal tumor | Reference (first author, year)      |
|-------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|---------------------------|---------------------------------|-------------------------------------|
| CAH HSD3B2 deficiency   | 41 years, poor compliance                                                                                                                                            | –             | +                         | +                               | Paula, 1994 (16)                    |
| CAH                     | 2 years, undiagnosed CAH/ laparoscopic right salpingo-oophorectomy and left adrenalectomy                                                                            | –             | +                         | –                               | Claahsen-van der Grinten, 2006) (8) |
| CAH                     | 15 years, poor medical control/ Laparoscopy with biopsy of both ovaries clinically controlled with only dexamethasone 0.75mg; small remnants of adrenal-like tissue. | –             | + (simple virilizing CAH) | –                               | Russo, 1998 (17)                    |
| CAH 21-OHase deficiency | 36 years, progressive virilizing symptoms/Bilateral oophorectomy 6 months after after left partial oophorectomy                                                      | –             | +                         | +                               | Al-Ahmadie, 2001 (18)               |
| CAH 11-OHase deficiency | 26 years, poor compliance/ Resection of bilateral ovarian mass. Right than left tumor, 8 months later.                                                               | –             | –                         | +                               | Luton, 1991 (19)                    |
| CAH 11-OHase deficiency | 8.7 years, female raised as a boy, bone age 17 years, increased pigmentation/Bilateral salpingo-oophorectomy and hysterectomy                                        | –             | +                         | +                               | Bas, 2000 (20)                      |
| CAH 21-OHase deficiency | 18 years, virilizing symptoms and hyperpigmentation after bilateral adrenalectomy/FDG PET-CT right ovarian uptake-Laparotomy, removal of right ovarian mass          | +             | +                         | –                               | Tiosano 2010) (10)                  |
| CAH 21-OHase deficiency | 17 years 4 years after bilateral adrenalectomy/ Right than left adnexectomy                                                                                          | +             | +                         | +                               | Present case                        |
| CAH                     | 7 years, 1 year after right adrenalectomy                                                                                                                            | +             |                           | –                               | Motlik, 1973 (22)                   |
| <b>Cushing Syndrome</b> |                                                                                                                                                                      |               |                           |                                 |                                     |
| Nelson's syndrome       | 35 years, 11 years after bilateral adrenalectomy/laparotomy                                                                                                          | +             | +                         | –                               | Baranetsky, 1979 (21)               |
| Nelson's syndrome       | 39 years, 14 years after bilateral adrenalectomy/laparotomy                                                                                                          | +             | +                         | –                               | Verdonk, 1982) (15)                 |
| Cushing's syndrome      | 2 years, precocious pseudopuberty/ removal of the mass                                                                                                               | –             | –                         | –                               | Adeyemi, 1986) (11)                 |

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