

Ovarian Adrenal Rest Tumors Undetected by Imaging Studies and Identified at Surgery in Three Females with Congenital Adrenal Hyperplasia Unresponsive to Increased Hormone Therapy Dosage

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Abstract Patients with congenital adrenal hyperplasia have a predisposition for developing adrenal rest tumors. In contrast to testicular adrenal rest tumors, ovarian adrenal rest tumors are less common, and only a few cases have been reported in the literature. This report presents three Chinese female congenital adrenal hyperplasia patients (9 to 15 years of age) with small ectopic adrenal cortical nodules that were not detected by imaging but were diagnosed at surgery. All three patients developed virilization with elevation of 17-hydroxyprogesterone, androstenedione, and androgen levels despite receiving maximum adrenal hormone replacement therapy. Ultrasound and magnetic resonance imaging of the abdomen and pelvis suggested bilateral expansion of the adrenal glands, but no lesions of the ovaries were observed. Laparoscopy and/or laparotomy revealed small nodular lesions surrounding the pelvic gonad in all three cases. Histopathological examination of the resected tissue in all cases revealed hyperplastic nodules of cells surrounded by fibrous tissue. The cells were arranged as nests with abundant cytoplasm, which were partially lightly stained with a small centered nucleus. Immunohistochemistry staining revealed the cells to be synaptophysin positive, melan-A positive, and chromogranin A negative, indicating the cells were adrenocortical tissue and not adrenal medullary cells. Thus, the findings of the histopathological examination

were consistent with ovarian adrenal rest tumors. Female congenital adrenal hyperplasia patients with virilization who showed an inadequate response to hormone therapy and had negative imaging results may benefit from laparoscopic examination or laparotomy in order to confirm the diagnosis of ovarian adrenal rest tumors while receiving unilateral subtotal adrenalectomy or subtotal bilateral adrenalectomy.

Keywords Adrenal rest tumor · Ovarian adrenal rest tumor · Congenital adrenal hyperplasia · Laparoscopy

Introduction

Adrenal rest tumors (ARTs) occur when residual adrenal gland tissue forms benign, expanding nodules in the gonads and other locations of male and female congenital adrenal hyperplasia (CAH) patients. They have been well documented in male patients as testicular adrenal rest tumors (TARTs), with an incidence up to 94 % [1]. TARTs are easily imaged by ultrasound and magnetic resonance imaging (MRI) studies [2]. Increasing the dosage of hormone therapy can cause early TART lesions to shrink or completely resolve, while advanced lesions may require surgical removal [3]. Although female CAH patients can also develop ARTs, namely ovarian adrenal rest tumors (OARTs), the condition is believed to be very rare [4]. Clinical studies of this condition have not been performed, and only a few case reports have been published [5, 6].

A poor response to hormone replacement therapy is sometimes seen in female CAH patients. These patients may require several times the normal dose of replacement hormone in order to avoid hyperandrogenemia, and the increased dosing can result in various complications and poor compliance. Without an increase in hormone dosage,

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the hyperandrogenemia can severely affect physical development and cause irreversible damage to female gonadal function, similar to that seen in male CAH patients [7]. Unlike their male counterparts, female CAH patients unresponsive to hormone replacement therapy are rarely diagnosed with ARTs. OARTs are seldom revealed with standard imaging techniques, making their diagnosis and subsequent treatment difficult. Without alternatives, endocrinologists often resort to subtotal adrenalectomy with minimal therapeutic benefit.

In this report, we present three cases of female CAH patients with small OART nidi that were undetected by imaging studies but were diagnosed by histopathological evaluation of surgical specimens following abdominal exploration.

Case Reports

This study was approved by the Institutional Review Board of the hospital, and all patients provided assent and their legal guardians provided written informed consent for their case data and images to be published.

Case 1

A 9-year-old female with a history of ambiguous sexuality and enlarged clitoris at birth and subsequent diagnosis of salt-wasting CAH presented with virilization, deepening voice, profuse acne, and muscle rigidity for 6 months. In the beginning, because her parents did strictly supervise her on taking medication, the patient forgot medication sometimes and was therefore partially noncompliant with the prescribed hormone replacement therapy. When she started to show signs of masculinity, the endocrinologist adjusted the amount of hormones and repeatedly emphasized the importance of regular medication to her parents, who realized and then started to strictly supervise the kid to take the medication every day.

Laboratory testing revealed elevated androgen, 17-hydroxyprogesterone, and androstenedione levels (Table 1). The daily hormone dosage was increased. Based on a weight of 38.5 kg and body surface area of 1.22 m², a dosage of 10 mg hydrocortisone per day plus 5 mg of prednisone per day plus 0.1 mg of fludrocortisone per day, converted to hydrocortisone, resulted in a total daily dosage of hydrocortisone of 31.5 mg per day. Her clinical symptoms and endocrine indicators did not improve after the increased hormone dosage, and she developed Cushing's syndrome. With a suspicion of OARTs, ultrasound and MRI of the abdomen and pelvis were performed, and *bilateral adrenal gland hyperplasia* was detected with no abnormal nidi. The patient's parents refused a higher dose of hormone therapy, and a unilateral total adrenalectomy was scheduled. Laparoscopic examination of the pelvic cavity revealed several slender nodules on the bilateral

ovaries and attached tissue (Fig. 1). Laparotomy was performed to determine whether additional small nodules were present. Palpation during surgery confirmed multiple small nodules on the ovaries and attached tissue, and five suspicious nodules with diameters <0.5 cm were removed (Fig. 2). Since lesions suspected to be OARTs were found, adrenalectomy was not performed.

Histopathological examination of the resected tissue revealed hyperplastic nodules of cells surrounded by fibrous tissue in three of the five nodules (Fig. 3). The cells were arranged in a nest and organ shape with abundant cytoplasm, partially lightly stained, and a small centered nucleus. Immunohistochemistry staining using the EnVision method and 3,3'-diaminobenzidine (DAB) was performed with antibodies for melan-A (Fig. 3d), α -inhibin (Fig. 3e), and chromogranin A (CgA) (Fig. 3f). Three of the five nodules were positive for both melan-A and α -inhibin, and negative for chromogranin A, indicating the cells were adrenocortical tissue and not adrenal medullary cells (Fig. 3).

Case 2

A 15-year-old female was diagnosed at age 11 with simple virilizing CAH following an abnormal gain in height and lack of breast development and menarche; she was prescribed oral hormone replacement therapy. Laboratory testing revealed elevated androgen, 17-hydroxyprogesterone, and androstenedione levels (Table 1). Ultrasound and MRI of the abdomen and pelvis revealed *bilateral adrenal gland hyperplasia*, but no abnormal nidi were detected. The daily hormone dosage was increased. Based on a weight of 58 kg and body surface area of 1.61 m², a dosage of 20 mg of hydrocortisone per day plus 0.75 mg of dexamethasone per day plus 0.1 mg of fludrocortisone per day, converted to hydrocortisone, resulted in a total daily hydrocortisone dosage of 41.5 mg. The patient was unresponsive to the increased hormone dosage. At laparoscopy, multiple small nodules on the ovaries and attached tissue were identified, and five suspicious nodules (0.5 to 0.8 cm in diameter) were removed. Adrenalectomy was not performed. Histopathological and immunochemistry staining results of one of the five nodules were similar to that seen in case 1: hyperplastic nodules of cells surrounded by fibrous tissue were present, and immunohistochemistry staining indicated the nodule was composed of adrenocortical tissue with no medullary tissue identified.

Case 3

A 9-year-old female with a history of salt-wasting CAH diagnosed shortly after birth was placed on hormone replacement therapy and evaluated at routine visits. At the age of 8 years, the patient presented with abnormal endocrine function including elevated androgen, 17-hydroxyprogesterone, and

Table 1 Patient data

	Case 1	Case 2	Case 3
Age (years)	9	15	9
CAH type	Salt-wasting	Simple virilizing	Salt-wasting
Clinical symptoms	Obvious masculinization	Obvious masculinization, no breast development, amenorrhea	Obvious masculinization
Hormone dosage	> 20 mg/m ² /d	> 20 mg/m ² /d	> 20 mg/m ² /d
Ultrasound	No lesions suspicious for OART	No lesions suspicious for OART	No lesions suspicious for OART
MRI	No lesions suspicious for OART	No lesions suspicious for OART	No lesions suspicious for OART
Lesions/suspicious nodules at surgery	3/5	1/5	3/8
Size of lesions (cm)	0.3, 0.3, 0.4	0.5	0.5, 0.8, 0.5

CAH, congenital adrenal hyperplasia; OART, ovarian adrenal rest tumor; MRI, magnetic resonance imaging

androstenedione levels (Table 1). The daily hormone dosage was increased. Based on a weight of 31 kg and body surface area of 1.07 m², a dosage of 20 mg of hydrocortisone per day plus 0.1 mg of fludrocortisone per day, converted to hydrocortisone, resulted in a total daily hydrocortisone dosage of 21.5 mg. Increased hormone therapy failed to inhibit hyperandrogenemia. Ultrasound and MRI of the abdomen and pelvis were negative for abnormal nidi. Diagnostic laparoscopy revealed eight suspicious nodules (0.5 to 0.8 cm in diameter), which were removed. Adrenalectomy was not performed. Histopathological examination and immunohistochemical staining results of three of the eight nodules were identical to that of the other two cases.

Follow-up

The follow-up endocrinologic test results (4 years after surgery) are shown in Table 2.

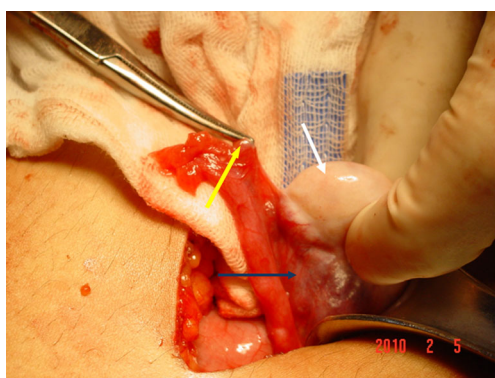


Fig. 1 Case 1. Laparoscopic examination of the pelvic cavity revealed several slender nodules on the bilateral ovaries and attached tissue. The forceps and the yellow arrow indicate the suspicious OART lesion (confirmed by histology in Fig. 3). White arrow, ovary. Blue arrow, broad ligament

Case No. 1 Postoperative endocrinologic investigation showed no significant improvement, nor there was obvious improvement in the masculinizing signs. Reexamination was suggestive of significant adrenal hyperplasia, and we recommended adrenal gland surgery; this was rejected by the patient's family. Hormone therapy was continued at the same dose as before surgery. The patient is now in puberty but has no menstruation or breast development.

Case No. 2 The patient was in puberty at the time of surgery but had no menstruation or breast development. Her skin was rough, with acne all over her body. The patient showed a good postoperative effect, with gradual restoration of endocrinologic testing results to normal levels. Menarche occurred 1 year after surgery. Her breast development proceeded normally after surgery. Her skin became lighter and smoother with the appearance of female sexual characteristics. We were able to gradually reduce her hormone dosage.

Case No. 3 Surgery resulted in improvement of her clinical symptoms, but the endocrinologic markers were not

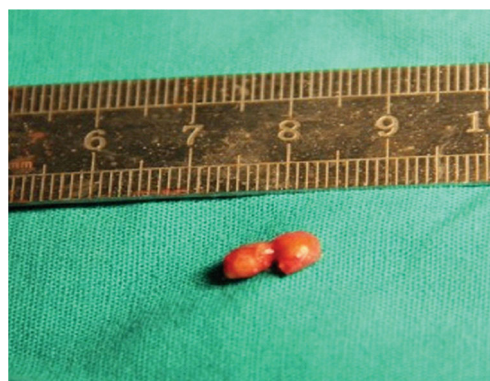


Fig. 2 Case 1. Resected nodule suspicious for an ovarian adrenal rest tumor (OART)

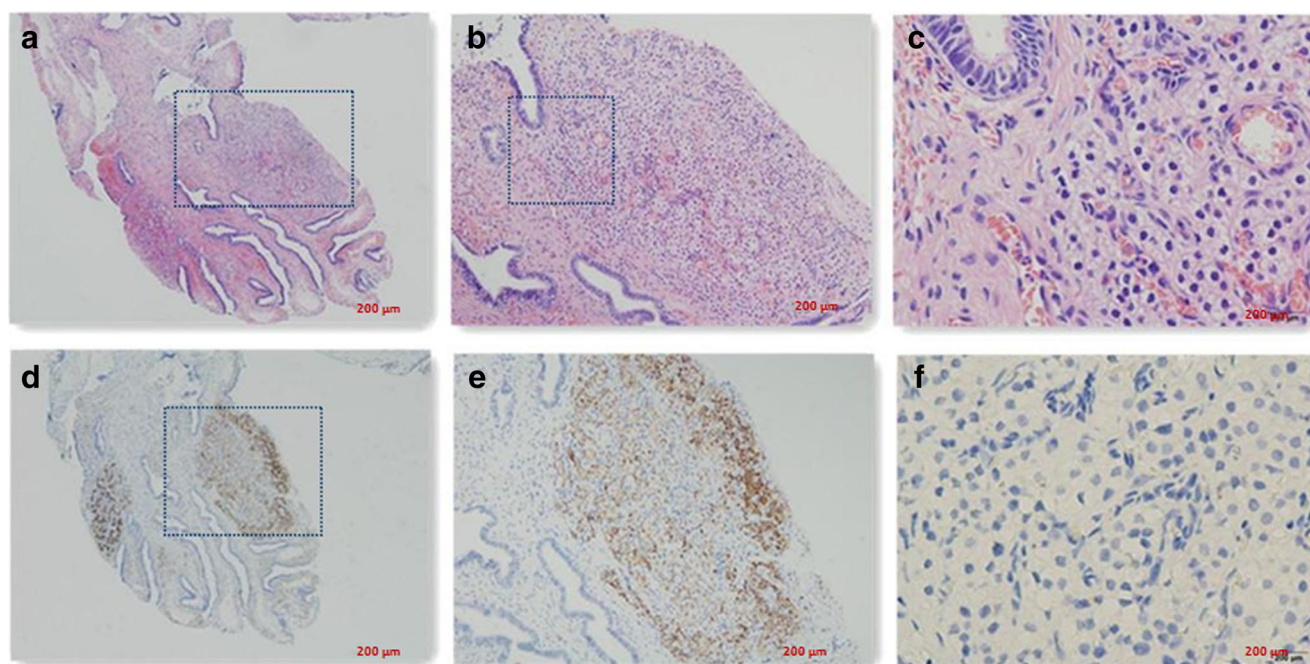


Fig. 3 Histopathological examination and immunohistochemical staining of an OART nodule removed in patient no. 1. **a–c** Hematoxylin and eosin staining at $\times 40$, $\times 100$, and $\times 400$ magnification, respectively. The cells are arranged in a nest-and-organ shape with

abundant cytoplasm, partial light staining, and a small centered nucleus. **d, e** Melan-A immunohistochemistry ($\times 40$) and alpha-inhibin positive staining ($\times 100$), respectively, suggestive of adrenal gland cortical cells. **f** Negative Cg-A staining ($\times 400$), suggesting nonadrenal medullary cells

satisfactory, with *evident adrenal hyperplasia* at reexamination. A left adrenalectomy was performed 1 year after the original surgery. At reexamination 3 years later, her laboratory results showed basically normal endocrinology. She

underwent menarche, and we were able to reduce her hormone dosage.

Table 2 Comparison of endocrinologic examination results before surgery (before and after drug treatment) and 4 years after surgery

		Case 1	Case 2	Case 3
T (ng/mL)	Before drug treatment	9.29	8.15	2.02
	After drug treatment	9.1	7.95	1.97
	Follow-up (4 years)	0.85	<0.10	<0.13
A (nmol/L)	Before drug treatment	>35	>35	>35
	After drug treatment	>35	>35	>35
	Follow-up (4 years)	18.3	3.92	2.13
17-OHP (ng/mL)	Before drug treatment	>20	>20	>20
	After drug treatment	>20	>20	>20
	Follow-up (4 years)	>20	5.98	5.75
FSH (IU/L)	Before drug treatment	4.61	6.2	0.61
	After drug treatment	3.73	6.23	0.33
	Follow-up (4 years)	5.89	6.59	3.79
LH (IU/L)	Before drug treatment	1.41	1.97	0.15
	After drug treatment	1.77	1.84	0.26
	Follow-up (4 years)	2.34	17.3	1.99

Reference ranges: T, 0.09–1.30 ng/mL; A, 1.00–11.50 nmol/L; 17-OHP, 0.50–2.10 ng/mL; FSH, 5–22 IU/L; LH, 24–105 IU/L

T testosterone, A androstenedione, 17-OHP 17-hydroxyprogesterone, FSH follicle-stimulating hormone, LH luteinizing hormone

Discussion

None of our three patients had undergone adrenal surgery at the time of their first visit with us. High-dose hormone therapy had no treatment effect but instead resulted in complications of excess hormone therapy. Because preoperative imaging failed to show any suspicious OART lesions, the pediatric endocrinologist recommended unilateral or bilateral subtotal adrenal resection in all three patients. All patients had either obvious or suspicious OART lesions on examination during laparoscopy, and we therefore made the decision to excise these small lesions rather than completing the originally planned adrenalectomy.

The second patient showed the best postoperative follow-up results, with the appearance of female sexual characteristics and a lesser degree of adrenal hyperplasia after surgery. In comparison, the first and third patients had worse postoperative outcomes following the removal of OART lesions, with significant adrenal hyperplasia. A second surgery for adrenalectomy was recommended to these two patients. The first patient rejected the reoperation, even though she had endocrine abnormalities and obvious muscularity present. The third patient underwent adrenalectomy at 1 year after the original surgery and achieved a better outcome.

The results show that only one case (no. 2) had significant improvement following the removal of OARTs and did not need the adrenal surgery, while in two cases (no. 1 and no. 3), adrenalectomy was required after the first surgery (not performed in case no. 1 because of the parental rejection). Thus, it suggests that adrenalectomy might have been performed together with the resection of the OART lesions to avoid a second surgery. This notion needs to be tested in more clinical cases. Adrenal hyperplasia does not appear to be an accurate indication of adrenalectomy, because significant adrenal hyperplasia was detected in all cases either before or after the first surgery.

In 1940, Wilkins et al. [8] first reported the relationship between ARTs and CAH and proposed that ARTs were benign growing nodules resulting from residual adrenal gland tissue in the gonads and related tissues of CAH patients. ARTs have been shown to be especially prevalent in salt-wasting CAH patients [9]. Although the exact origin of the cells is still under debate, the proximity of the adrenal glands and gonads during embryonic development supports a theory of ectopic migration of residual adrenal cortex cells into the developing gonads within the retroperitoneal region [10]. In this case series of three OART patients, the histological evidence supports the proposed theory that ARTs arise from developing adrenal gland tissue since the biopsied adrenal cortex tissue had secretory function but lacked medullary tissue.

Most TARTs occur in the testis, but rare cases have been reported in extra-testicular locations [11]. The most common presentation is bilateral lesions, with a severe mass effect on the testes due to enlargement of the nidus. TARTs are well reported in the medical literature with a general consensus regarding their diagnosis and treatment. Male CAH patients should routinely receive an ultrasound and palpation examination [12], and following these procedures, TARTs are usually diagnosed early [13]. An increased dosage of hormone therapy can cause early TART lesions to shrink or completely resolve, and advanced lesions may be removed surgically [3].

Unlike TARTs, little is known concerning OARTs. Al-Ahmadie et al. [14] reported the first case of an OART in 2001, followed by a few single case reports. One report described a 4-month-old female patient hospitalized with vomiting and failure to thrive; she had clitoromegaly, pigmented skin that was most prominent around the nipples, and abnormal serum sodium and potassium levels. Since a diagnosis of CAH due to 21-hydroxylase deficiency was presumed, treatment with corticosteroids and fluid replacement was begun, but the patient died 1 day later. Histopathology examination of the ovaries found multiple nodules ≤ 0.5 cm in diameter, in close proximity to one another and with cells resembling adrenocortical zona reticularis cells. The histopathology of the nodules was the same as the hyperplastic adrenal cortex [15].

Thomas et al. described a 17-year-old female who was diagnosed with congenital adrenal hyperplasia with 21-hydroxylase deficiency at birth and had delayed onset of menses, virilization, and psychiatric issues. She was treated with dexamethasone and Florinef, but noncompliance with treatment led to elevated testosterone and 17-hydroxyprogesterone levels. A screening ultrasound and MRI revealed a 5-cm mass in the left ovary. Diagnostic laparoscopy found a smaller mass on the right ovary in addition to the large mass on the left ovary. Histologically, the nodules were composed of closely packed, round to polygonal cells with vacuolated to eosinophilic cytoplasm and distinct cell borders, and they were separated by granular pigment. The tumor cells had immunoreactivity for alpha-inhibin, melan-A, and calretinin. The tumor fulfilled the WHO criteria for steroid cell tumor, not otherwise specified [16]. It has been generally accepted that OARTs are extremely rare. Researchers have suggested the low incidence of OARTs is due to primary sex cord regression, including all aberrant adrenal cells, during gonad development [17]. Early in embryological development, the gonadal ridge can develop into a male or a female gonad, and in both males and females, primary sex cords are formed from the mesonephric duct. In males, the primary sex cords become the rete testis and seminiferous tubules, and aberrant adrenal cells may be present. In females, the primary sex cords regress, and thus, aberrant adrenal cells located in the primary sex cords will also regress.

Stikkelbroeck et al. [4] applied the same imaging techniques (ultrasound and MRI) were successful in locating TARTs to a group of 13 female CAH patients, and when neither method revealed unusual nidi, the authors concluded that the occurrence of OARTs was very rare. In the current report, three female CAH patients with an inadequate response to traditional hormone replacement and no detectable nidus underwent surgery, and slender, suspicious nidi around the gonads were identified and biopsied. The nodules had diameters <0.8 cm and were similar to TARTs in appearance. The resected nodules were a light yellow color with lobulated margins and a hard texture. These features were similar to the resected lesions in the male CAH patients treated at our center. Histopathological studies revealed adrenocortical cells, confirming a diagnosis of OARTs. These findings suggest that OARTs are more common among female CAH patients than previously described, especially in patients unresponsive to hormone replacement therapy; the view that OART is very rare may be the result of the inability to visualize smaller nidi by current imaging techniques. Crocker et al. [18] used 18F-FDG PET/CT with cosyntropin stimulation to accurately identify adrenal rest tissue not visualized with conventional imaging in a female with salt-wasting 21-hydroxylase deficiency who had a bilateral adrenalectomy at age 17 years and presented with hyperandrogenism at age 32 years. The wider use of this technique may improve the ability to diagnose OARTs.

The primary limitation of this report is the small number of cases. Though OARTs may be more common than previously described, they are still an uncommon occurrence.

Conclusions

We recommend exploration of the adnexae and excision of any OART lesions found in female CAH patients who respond poorly to hormone therapy and in whom preoperative imaging fails to show suspicious OART lesions. This strategy may alleviate some of the patients' symptoms. For patients with poor postoperative outcomes and obvious adrenal hyperplasia, a unilateral adrenalectomy may then be undertaken and may yield good results.

Consent

Written informed consent was obtained from the patients for publication of these case reports and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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Authors' Contributions We declare that all the listed authors have participated actively in the study and all meet the requirements of authorship. Dr. JCL designed the study and wrote the protocol and performed the research/study. Dr. HDC wrote the first draft of the manuscript and performed the research/study. Dr. LH performed the research/study. Dr. ZHZ and Dr. ZS managed the literature searches and analyses. Dr. HJ undertook the statistical analysis. Dr. JZ was responsible for the immunohistochemical examinations. All authors read and approved the final manuscript.

Compliance with Ethical Standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of Interest The authors declare that they have no conflict of interest.

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