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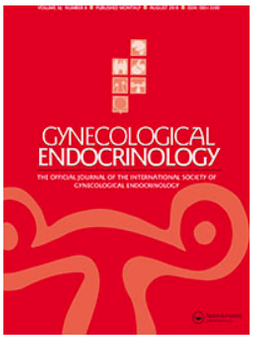

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PARA-OVARIAN ADRENAL REST TUMOR

Para-ovarian adrenal rest tumors: gynecologic manifestations of untreated congenital adrenal hyperplasia

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ABSTRACT

Congenital adrenal hyperplasia (CAH) is an inherited disorder of adrenal steroidogenesis often diagnosed in infancy. Gynecologists may encounter adult patients with CAH due to the clinical effects of increased androgens, e.g. hirsutism, clitoromegaly, oligomenorrhea, or, rarely, pelvic masses. This case report reviews the association of para-ovarian adrenal rest tumors with CAH, and the role of gynecologists in their evaluation and treatment. A 23-year-old woman with CAH (21-hydroxyase deficiency) untreated for the past 5 years presented with a pelvic mass and elevated serum testosterone (1433 ng/dL) and plasma ACTH (1117 pg/mL). Intraoperative findings revealed multiple retroperitoneal masses. Final pathology demonstrated adrenal rest tissue. Para-ovarian and ovarian adrenal rest tumors may present as a rare gynecologic manifestation in patients with untreated CAH.

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Pelvic mass; ovary; adrenal gland; adrenal hyperplasia

Introduction

Congenital adrenal hyperplasia (CAH) refers to a group of autosomal recessive disorders of adrenal steroid biosynthesis that may have varying gynecologic manifestations. Mutations in the *CYP21A2* gene leading to deficient or absent activity of the 21-hydroxylase enzyme account for 95% of cases of CAH leading to inadequate glucocorticoid and often mineralocorticoid production, with a concomitant increase in androgens and steroid intermediates [1]. In the virilizing subtype of 21-hydroxylase deficiency, affected females present as neonates with ambiguous genitalia [2], clitoral enlargement, and a common urogenital sinus. Diagnosis in the "salt-wasting" subtype of 21-hydroxylase deficiency may also occur after an adrenal crisis with patients presenting with hyponatremia, hyperkalemia, and/or dehydration [2]. In milder forms or undertreated severe forms of 21-hydroxylase deficiency, gynecologists may encounter adolescent and adult female patients who present with manifestations of increased androgens, e.g. hirsutism, clitoromegaly, oligomenorrhea, infertility, decreased breast mass, or, as in our case, a pelvic mass.

Case

A 23-year-old female with CAH secondary to 21-hydroxylase deficiency was diagnosed soon after birth. She had a history of noncompliance since the start of adolescence, with neither glucocorticoid nor mineralocorticoid therapy for the last 5 years. She presented to the Emergency Department with generalized abdominal pain. Laboratory evaluation at that time revealed multiple abnormalities secondary to medication noncompliance: ACTH: 1117 pg/mL (6–58), testosterone: 1433 ng/dL (female: 14–76; male: 270–1070), and 17-hydroxyprogesterone: 9480 ng/dL (normal follicular: 15–70, luteal: 35– 290). Sodium and potassium levels were normal during this event (143 and 4.3 mEq/L, respectively). Transvaginal ultrasonography revealed a 6 cm left pelvic mass in a deep retroperitoneal location with a well-defined echogenic wall and compression of the left external iliac vein (Figure 1). The sonographic impression was a desmoid-type mass, fibroma, or possible lymphoma. A computerized tomographic scan performed one week prior to an outside facility had demonstrated the left adnexal mass, no lymphadenopathy, and normal-appearing adrenal glands.

The patient was then referred for a Gynecology Oncology consultation. At that time, she reported secondary amenorrhea during the aforementioned 5-year period of noncompliance. Her physical examination was consistent with elevated plasma ACTH and hyperandrogenemia: skin hyperpigmentation, clitoromegaly, and decreased breast tissue. Her pelvic examination revealed her prior vaginal reconstruction: narrowed vaginal introitus, clitoroplasty, and vaginoplasty. No masses were palpable on recto-vaginal examination. She was scheduled for removal of the pelvic mass for tissue diagnosis. Endocrinology consultation was obtained due to her steroid noncompliance and concern for operative/post-operative adrenal insufficiency. Accordingly, she received pre-operative stress-dose hydrocortisone treatment.

The patient underwent an exploratory laparotomy, resection of bilateral retroperitoneal masses, and left external iliac lymph node sampling. Intra-operative findings revealed a 6 cm left retroperitoneal left adnexal mass overlying the left external iliac artery, three lesions overlying the right ovarian vessels, and a 5 cm right-sided mass within the broad ligament. Her ovaries appeared grossly normal; therefore, neither salpingo-oophorectomy nor ovarian tissue biopsy was performed. Frozen pathology was indeterminate. Due to the patient's age, fertility-sparing treatment was considered and the procedure terminated to await final pathology.

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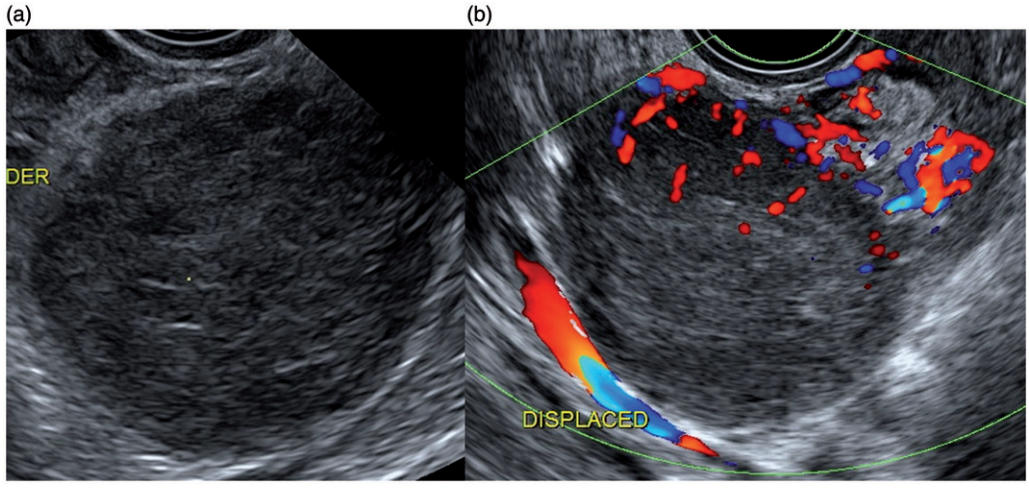

Figure 1. Ultrasonographic appearance of a para-ovarian adrenal rest tumor demonstrating an echogenic border (a), increased blood flow, and compression of the external iliac vein (b).

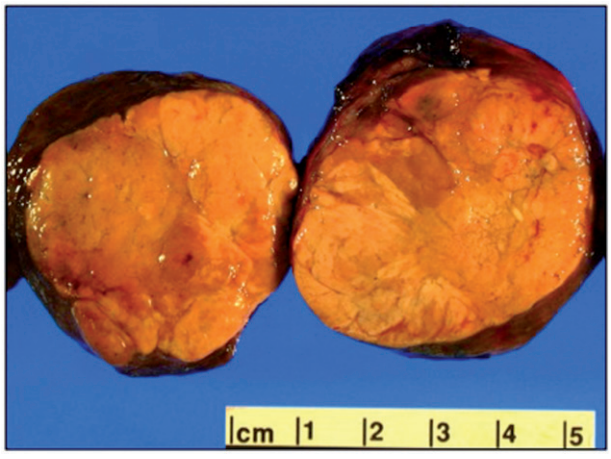

Figure 2. Para-ovarian adrenal rest tumor.

Gross examination of all of the specimens revealed multiple lobulated yellow-tan masses surrounded by a rim of brown-gray tissue (Figure 2). Each lesion was well-circumscribed, surrounded by a fibrous capsule containing nests of polygonal cells intersected by fibrous septae. Histologic examination demonstrated bubbly abundant eosinophilic cytoplasm with eccentric nuclei admixed with a lymphocytic infiltrate. There were no mitotic figures, and the lymph node was also benign. Consultation with the pathology department at Stanford University confirmed multifocal adrenocortical proliferation, consistent with a final diagnosis of para-ovarian adrenal rest tumors.

Despite provisions of the above hydrocortisone dose for the first operative day, the patient's post-operative course was complicated by hypotension and hyperkalemia, which responded to intravenous fluid resuscitation. These abnormalities were likely due to inadequate mineralocorticoid replacement in the post-operative period. She was then re-initiated on an age-appropriate oral glucocorticoid and mineralocorticoid regimen, and discharged home on post-operative day three in stable condition.

Discussion

Adrenal rest tumors are extra-adrenal foci of adrenal tissue. These are commonly found in the testes of male patients with poorly controlled CAH and are known as testicular adrenal rest tumors (TARTs) [2]. The incidence of TARTs in male patients with CAH can be significant, with a prevalence ranging from 14 to 55% in boys and young adults [2–4].

Ovarian adrenal rest tumors (OARTs) have also been reported, but are very rare with less than 20 documented cases in the literature. Even less often, adrenal rest tumors have been found in the para-ovarian and adnexal areas. A literature search by Zaarour et al. in 2014 revealed a total of 12 documented cases of ovarian and para-ovarian ART, most commonly associated with elevated plasma ACTH levels in women with CAH [5]. Nine of these patients had OARTs, while three had para-ovarian adrenal rest tumors. Two of the patients with para-ovarian masses had elevated ACTH secondary to Nelson syndrome, but not CAH. Chen, et al in 2016 reported three other cases of OARTs in patients with CAH [6]. Our literature search also included an additional OART case documented in 2011 [3]. To our knowledge, our patient would be the fourth para-ovarian adrenal rest tumor documented by pathology in the literature.

Two theories exist to explain the etiology of adrenal rest tumors. The first is that aberrant adrenal tissue descends with the gonads versus the second theory that pluripotent gonadal cells are stimulated by excess circulating ACTH. The adrenal glands share a common embryonic origin with the early gonad known as the adreno-genital primordium [7,8]. As the adrenal glands develop near the gonads, some adrenal tissue may become adherent and descend with and within the testis or the ovary [1,7]. The first theory is supported by inguino-scrotal surgeries of young boys where ectopic remnants of adrenal cortex were incidentally found along the spermatic cord during these procedures [7]. In females, adrenocortical tissue has been identified in the broad ligament and adnexa [8]. Animal models support the second theory where adrenal-like cells, which express adrenal markers and respond to ACTH, have been found within mouse testes [1]. Studies on pups with adrenal aplasia have also corroborated this theory. Affected female pups die due to adrenal insufficiency, while male pups survive secondary to glucocorticoid production from adrenal-like cells in the testes [9,10]. The authors, however, caution extrapolation to human models due to the presence of ACTH receptors in animal, but not human testes [1].

With respect to ovarian and para-ovarian ARTs, the most common etiology is thought to be secondary to sustained ACTH production. In poorly compliant patients with CAH, ACTH

hypersecretion may activate adrenal rest tumor development [1,7]. In a reciprocal fashion, OARTs undetected by imaging studies have also been diagnosed at the time of surgery in CAH patients unresponsive to increasing hormonal therapy [6].

During the work-up of these masses, TARTs in males are often easily visualized; however, in females, a diagnosis may prove challenging, as conventional imaging may not demonstrate ovarian or para-ovarian adrenal rest tumors [6]. As in our case, the patient had multiple masses, only one of which was demonstrated with multiple imaging modalities. When detected by ultrasonography, the lesions will usually appear as homogenous, hypoechoic masses [11]. Some authors propose the use of MRI for improved contrast resolution and identification of disease extent [11]. In patients with CAH after adrenalectomy, ^{18}F-labeled fluoro-2-deoxy-d-glucose PET/CT scan after cosyntropin stimulation has been used to identify ectopic adrenal tissue in females [5,7]. Of note, a complete imaging evaluation in these cases is essential to rule out concurrent adrenal pathology. Although our patient's adrenal glands were reported as normal in size, for non-compliant patients, a degree of adrenal hyperplasia and/or enlargement would have been expected.

There is currently no standardized treatment protocol for adrenal rest tumors in females due to the rarity of these masses. The majority of patients in the literature underwent unilateral or bilateral salpingo-oophorectomy, possibly due to unfamiliarity with the association between CAH and OART, or concern for malignancy [3]. For younger patients, such as our case, fertility-sparing surgery may be considered, such as diagnostic laparoscopy and ovarian biopsy to confirm adrenal tissue followed by steroid treatment. With respect to medical therapy, the impact of glucocorticoid therapy on the resolution of ovarian/para-ovarian adrenal rest tumors is unknown [5]. However, short-term courses of high-dose dexamethasone frequently cause significant shrinkage, and, in many cases, complete resolution of TARTs in males [6]. Theoretically, patients with small ovarian or para-ovarian adrenal rest tumors may respond in a similar fashion [3,5]. Larger lesions, however, will likely necessitate surgical removal.

Conclusions

Ovarian/para-ovarian adrenal rest tumors can be a rare, benign gynecologic manifestation of untreated CAH in females. Although, malignancy is always included in the differential diagnosis for a young patient with an ovarian mass and elevated testosterone, for patients with untreated or poorly treated CAH and an adnexal mass, para-ovarian or ovarian ART should be higher on the differential diagnosis. Consultation with Gynecology Oncology is of utility given the rarity of these masses, while consultation with Endocrinology is essential for treatment optimization of patients with poorly treated CAH. Additional imaging is also critical to rule out adrenal pathology. Consideration of an initial short-term trial of high-dose dexamethasone should also be entertained given its success in males with analogous testicular tumors, which may then avoid surgery entirely.

Ethical approval

IRB exemption: Touro University Nevada IRB was consulted and ruled that approval was not required for this study.

Disclosure statement

The authors have no conflict of interest and nothing to disclose. No sources of financial support were needed.

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