A girl with steroid cell ovarian tumor misdiagnosed as non-classical congenital adrenal hyperplasia

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SUMMARY: Yılmaz-Ağladıoğlu S, Savaş-Erdeve Ş, Boduroğlu E, Önder A, Karaman İ, Çetinkaya S, Aycan Z. A girl with steroid cell ovarian tumor misdiagnosed as non-classical congenital adrenal hyperplasia. Turk J Pediatr 2013; 55: 443-446.

Ovarian steroid cell tumors are rarely encountered in prepubertal girls. The majority of these tumors produce hormones, testosterone being the leading one. These tumors may either coexist with or imitate congenital adrenal hyperplasia (CAH). We present a 13-year-old female patient who was diagnosed with non-classical CAH at six years of age while being investigated for premature pubarche. She was diagnosed with steroid cell ovarian tumor after a delay of six years. The diagnosis was based on radiologic imaging, which was performed to investigate causes of unsuccessful metabolic control while under high-dose steroid therapy. The right ovarian hypoechoic mass of 23x22 mm was excised laparoscopically, preserving the ovary. Immunohistochemical staining showed that tumor cells were strongly positive with inhibin and focally positive with vimentin. Based on these findings, the patient was diagnosed with ovarian steroid cell tumor not otherwise specified. In the postoperative second week, total testosterone level was <10 ng/ml, and 17-hydroxyprogesterone (17-OHP) level was 1.1 ng/ml. Peak 17-OHP level was 4.2 ng/ml on repeated ACTH stimulations, and the diagnosis of CAH was excluded. Steroid therapy was tapered down and then discontinued.

It should be kept in mind that there may be a misdiagnosis in cases of CAH, which may present itself with unsuccessful metabolic control even while under the appropriate treatment dose. Early diagnosis and treatment would prevent the development of irreversible signs.

Key words: steroid cell ovarian tumor, congenital adrenal hyperplasia, hyperandrogenism.

Steroid cell tumors account for 0.1% of overall ovarian neoplasms[1]. These tumors are usually seen in women of reproductive age. However, though rarely, they have been reported in postmenopausal women as well and in pediatric cases. The majority of these tumors secrete hormones, and patients with these tumors generally present with the clinical signs of excessive hormone secretion, such as virilization or feminization. It may coexist with or imitate virilizing congenital adrenal hyperplasia (CAH)[2].

A 13-year-old female patient, who was diagnosed with non-classic congenital adrenal hyperplasia (NCCAH) while being investigated for premature pubarche at the age of six years, is presented here. The patient was further investigated due to progressive virilization symptoms under steroid therapy and persistent high plasma total testosterone (TT) and 17-hydroxyprogesterone (17-OHP) levels. She was then diagnosed with steroid cell ovarian tumor. In this case report, the presented patient is also discussed in light of information in the literature.

Case Report

A 12-year-old girl was referred to our endocrine clinic for follow-up. Her history revealed that she had applied to another center for premature pubarche at the age of six years, and laboratory results revealed a basal 17-OHP level of 6

ng/ml. On ACTH stimulation test, 30th and 60th minute 17-OHP levels were 10 and 17 ng/ml, respectively. Based on these findings, she was diagnosed with NCCAH, so steroid therapy was started. During the follow-up period, she also received gonadotropin-releasing hormone agonist (GnRHa) due to central precocious puberty. The patient was receiving hydrocortisone at a dose of 15 mg/m^2 three times daily when she applied to our clinic.

At the time of admission, chronological age of the patient was 12 years, height was 146 cm (-1.5 SDS), and body weight was 48.6 kg (-0.4 SDS). Her thelarche was Tanner stage 4, and pubarche was Tanner stage 5. Genital examination revealed mildly enlarged clitoris of 1.5 cm. She had not begun menstruation. It was also observed that she had masculine muscle structure with increased muscle mass. She had severe hirsutism with Ferriman-Gallwey score of 12. Her parents also noted a deepening in the pitch of her voice.

Laboratory results were as follows: TT: 147 ng/dl, 17-OHP: 19.3 ng/ml, DHEA-S04: 112 μg/dl, ACTH: 7.17 pg/ml, luteinizing hormone (LH): 1.7 mIU/ml, follicle-stimulating hormone (FSH): 4.7 mIU/ml, and estradiol: 42 pg/ml. On her pelvic ultrasonographic examination, the uterus was 69 x 24 x 9 mm, the right ovary was 42 x 23 x 34 mm, and the left ovary was 41 x 30 x 41 mm and polycystic in structure. Because of high levels of 17-OHP and TT during treatment, hydrocortisone dose was increased to 20 mg/m^2/day. On her 6th month follow-up on therapy, TT was 215.92 ng/dl and 17-OHP was 95 ng/ml under the regular drug treatment. It was thought that there might be an underlying adrenal or ovarian tumor. Radiological imaging revealed normal adrenal ultrasonography (US) findings, but pelvic US revealed the uterus as 26x11x45 mm, left ovary as 30x18x39 mm, and right ovary as 25x16x30 mm with a lobular hypoechoic mass measuring 23x22 mm. The border of the mass could not be definitely distinguished from the lower pole of the right ovary. Laparoscopic mass excision was performed preserving the right ovary. No significant lymph node was noted intraoperatively. Macroscopic examination revealed a 2.5x2.3x2.1 cm solid, yellow tumor. Microscopic examination demonstrated a moderately pleomorphic neoplasm without mitoses or necrosis, which was surrounded by a fibrous capsule with the intact surrounding ovarian tissue. Immunohistochemical staining showed that tumor cells were strongly positive with inhibin and focal positive with vimentin. Based on these findings, the patient was diagnosed with ovarian steroid cell tumor not otherwise specified (NOS) (Fig. 1).

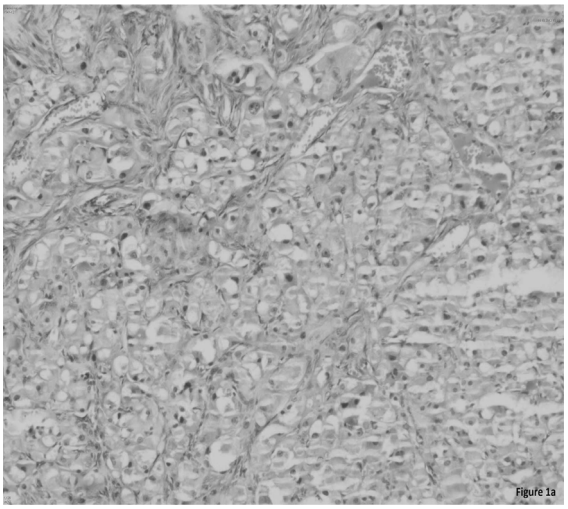
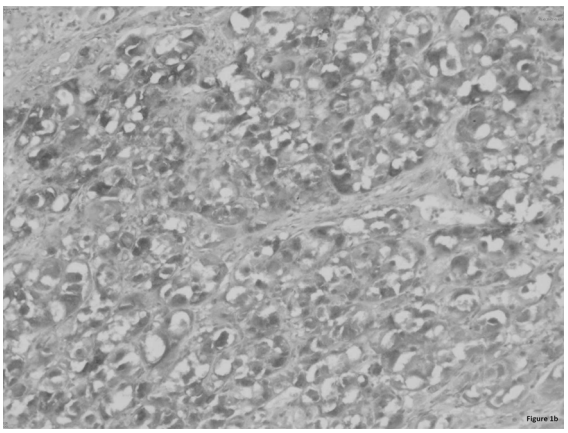
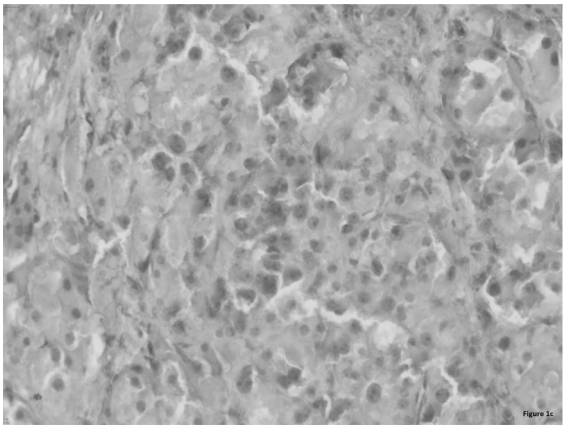


Fig. 1. Histopathology and immunohistochemistry showing: **a.** Moderately pleomorphic cells without mitoses or necrosis, which were surrounded by a fibrous capsule (hematoxylin & eosin x100).



b. Inhibin-positive in tumor cells (inhibin x100).

In the postoperative second week, TT level was <10 ng/ml, and 17-OHP level was 1.1 ng/ml. Steroid therapy was tapered down and then discontinued. Peak 17-OHP level was 4.2 ng/ml on repeated ACTH stimulation tests, and the diagnosis of CAH was excluded. Hirsutism was reduced, and menstrual cycles started spontaneously six months after the surgery.



c. Focal-positive vimentin in tumor cells (vimentin x100).

However, the deep voice persisted, and vocal cord surgery was planned. Table I demonstrates the changes in laboratory values at the time of diagnosis, before surgery and after surgery.

Discussion

Steroid cell ovarian tumors are one of the rarest tumors that cause virilization in children[3]. The origin of these tumors is debatable, and this terminology arises from the similarity of these tumors to steroid hormone-secreting cells[4]. There are three subtypes of steroid cell tumors: Steroid cell tumor NOS (60%), stromal luteoma (20%), and Leydig cell tumor (20%)[5]. Macroscopic appearance of the tumor may vary from small solid to large multicystic masses[6]. Pathologically, it is characterized by polygonal or round-shaped cells with definite border and large cytoplasm without Reinke crystals. They immunohistochemically show positive staining character for inhibin and vimentin (75%), antihuman cytokeratin (46%) and AE1/AE3 (37%). The majority of these tumors are hormonally active, and 75% present with hirsutism and virilization[4,5]. In the literature, it is mentioned that these tumors may clinically coexist with or imitate NCCAH, which may lead to delayed diagnosis[2]. Diagnosis of this present case with ovarian steroid cell tumor took seven years, after the patient was presented with premature pubarche at the age of six years. The case was imitating the clinical signs of NCCAH at presentation, and after making a diagnosis and resecting the tumor, it was determined that NCCAH had been misdiagnosed. Similar to our case, Azizlerli et al.[7] failed to provide a regression in virilization for eight years under glucocorticoid therapy in a case who was diagnosed with NCCAH based on virilization and accelerated growth. They could suppress ACTH, but failed to suppress testosterone and 17-OHP levels. They then diagnosed the case with ovarian steroid cell tumor NOS[7]. Baş et al.[2] diagnosed an 8.7-year-old patient with steroid cell tumor NOS who had CAH due to 11-beta hydroxylase deficiency with 46XX karyotype, and was raised as a boy. They reported that verification of CAH diagnosis was performed post-surgically by ACTH stimulation test[2].

Steroid cell tumors of the ovary are usually unilateral, and often very small, only slightly larger than the normal ovary on radiological imaging. Small steroid cell tumors are described as slightly hypoechoic or hyperechoic as compared to the ovary. It may be difficult to identify them on radiological imaging, in part because they are isoechoic to the uterus on ultrasound and isoattenuating on computerized tomography (CT)[8]. Moreover, it is difficult to localize the tumors smaller than 1 cm in

Table I. Changes in Laboratory Values and in Hydrocortisone Doses, at the Time of Diagnosis, Before and After Surgery

	At diagnosis (another hospital)	At admission to our hospital	Before surgery	Two weeks after surgery	Six months after surgery
Chronological age	6 yrs	12 yrs	12.5 yrs	13 yrs	13.5 yrs
Basal 17-OHP (ng/ml)	6	19.3	95	1.1	1.3
Peak 17-OHP (ng/ml)	17			4.7	
Total testosterone (ng/ml)	NA	147	215.92	<10	13
ACTH (3-46) pg/ml	NA	7.17	<5	46	60
Medical treatment	Hydrocortisone	Hydrocortisone	Hydrocortisone	Ø	Ø
Doses (mg/m^2/day)	15 mg/m^2/day	20 mg/m^2/day	Surgery	Ø	Ø

*NA: Not available.

diameter[7]. In this present case, the tumor may not have been visualized on pelvic US performed at the time of admission, but the size of her ovary was larger than normal for her age and was polycystic in structure. Because it was learned that the patient was diagnosed with central precocious puberty and followed for six years by another center, it was thought initially that the ultrasonographic sign was related to central precocious puberty. Nevertheless, when we reviewed the literature, we were confronted with case reports in which polycystic ovaries were observed on US, but the tumor could not be detected by US. They were detected only by CT and magnetic resonance imaging (MRI)[9]. Moreover, it is well known that GnRHa suppresses elevated androgen levels in patients with Leydig cell tumor. GnRHa may be an alternative choice to be considered as an adjuvant therapy for postoperative management of a persistent or recurrent hormone–producing steroid cell tumor of the ovary[10]. The presented patient also received GnRHa therapy for central precocious puberty. We believe that the therapy also contributed to the delay in the tumor diagnosis.

In all cases reported in the literature, hormone levels rapidly returned to normal levels within days following tumor resection, as in this present case. Little is known about the clinical courses and therapy responses of these tumors. Most of the cases are benign, unilateral and low-grade. Although it has been reported that benign steroid cell tumors may behave as malignant, no malignant tumor has been reported to date under the age of 20 years, and they were classically benign in childhood[11]. A conservative approach was preferred for this present case because there were no signs of malignant potential and no clean surgical border, and further fertility potential was considered. Neither relapse nor metastasis was detected postoperatively at the 6th month evaluation.

In conclusion, we considered this case worth presenting because steroid cell tumors are rarely encountered in childhood. In addition, this case has underlined that there may be misdiagnosis in CAH cases, which may present itself by unsuccessful metabolic control even at the appropriate treatment dose. This case also emphasizes the importance of early consideration of a tumor causing virilization. It should be kept in mind that tumors become larger in time, and may not be visualized initially. Early diagnosis and treatment would prevent development of irreversible signs, such as deep voice and short stature.

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