CASE REPORT

Virilization Secondary to Androgen-Secreting Tumor of the Ovary: A Report of Three Cases and Review of Literature

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Received: 30 November 2017 / Accepted: 26 December 2017 / Published online: 31 January 2018
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Introduction

Androgen-secreting tumors of the ovary represent < 5% of all ovarian tumors and are a rare cause (0.2% of cases) of androgen excess in females. They belong to the category of sex-cord stromal tumors; the most commonly implicated are Sertoli–Leydig cell tumors (SLCTs), Leydig cell tumors, steroid cell tumors, fibrothecomas and rarely granulosa cell tumors [1, 2]. Owing to their rarity, there is limited understanding of their natural progression and optimal management strategies. This report describes three cases and sheds light on diagnosis and treatment of these rare tumors.

Case Report

History and Examination

Three patients in different age groups, adolescent, early reproductive and perimenopausal age, presented to the

Fig. 1 Clinical features of Case 1. **a** Excessive facial hair, **b** clitoromegaly

outpatient department with signs and symptoms of severe and rapidly progressive hirsutism and virilization (Fig. 1) along with oligomenorrhea/amenorrhea. Past menstrual cycles were normal and regular in all patients. Case 2 was attempting unsuccessfully to conceive since last 1 year. Case 3 was multiparous, had three vaginal deliveries and had undergone laparoscopic tubal ligation 14 years ago. Past medical and surgical history was not contributory in any of the cases.

Body mass index (BMI) was normal except in Case 3 (overweight). None of the patients had Cushingoid features (moon facies, purple striae, buffalo hump), signs/symptoms of thyroid disorder or galactorrhea. Abdominal examination revealed no abnormality. Vaginal examination was avoided in Case 1 as she was unmarried; a small, non-tender, mobile adnexal mass was found in Case 2; no mass was palpable in Case 3.

Investigations

All patients had normal serum prolactin, serum thyroid stimulating hormone and morning cortisol levels. Markedly elevated total testosterone with normal dehydroepiandrosterone sulfate (DHEA-S) raised the suspicion of an ovarian androgen-secreting tumor in all three patients. The 17-hydroxyprogesterone (17-OHP) value was normal in all except Case 2; hence, she underwent an ACTH stimulation test to rule out late-onset congenital adrenal hyperplasia (CAH). All patients underwent a pelvic ultrasound (USG), which was majorly inconclusive. As there was strong suspicion of ovarian neoplasm, all patients underwent MRI which depicted presence of solid–cystic adnexal masses. None of the cases had any adrenal mass, ascites or lymphadenopathy. Cases 2 and 3 underwent FDG-PET CT (fluorodeoxyglucose positron emission tomography) which revealed hypermetabolic focus in the affected ovary which helped in confirming the diagnosis of androgen-secreting

ovarian tumor. Patient characteristics, serum hormonal profile and radiological investigations are outlined in Table 1.

Treatment

Cases 1 and 2 underwent unilateral salpingo-oophorectomy, laparoscopic and open, respectively, while Case 3 underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy. Intraoperatively, there were no ascites, lymphadenopathy or evidence of metastasis in any of the cases. The affected ovary was enlarged, while the contralateral ovary was normal in all cases (Fig. 2). Peritoneal washings and intraoperative frozen section did not reveal malignancy in any patient. Final histopathological diagnosis was Sertoli–Leydig cell tumor (well differentiated) in Case 1; steroid cell tumor not otherwise specified (NOS) in Case 2; pure Leydig cell tumor in Case 3. There was no evidence of atypia or malignancy in any tumor.

Follow-Up

Postoperatively, serum testosterone returned to normal in all three cases by day 7 and further decline was seen at 2 months post-surgery. The symptoms of virilization decreased gradually and regular menses resumed in case 1 and case 2 as hysterectomy is done in case 3 within 3 months of surgery. No recurrence was noted at 24, 12 and 18 months follow-up for Cases 1, 2 and 3, respectively.

Discussion

The three virilizing ovarian tumors diagnosed in our study belong to the group of ovarian sex-cord stromal tumors. Diagnosis of androgen-secreting tumors of ovary is confirmed by the characteristic clinical features and serum

Table 1 Patient characteristics and investigations

	Case 1	Case 2	Case 3
<i>Patient characteristics</i>			
Age (years)	17	23	46
Presenting symptoms and signs (modified Ferriman–Gallwey score)	Hirsutism (28) Hoarseness of voice Breast atrophy Clitoromegaly	Hirsutism (31) Hoarseness of voice Male pattern baldness Breast atrophy Clitoromegaly	Hirsutism (25) Hoarseness of voice Male pattern baldness
Menstrual symptoms	Amenorrhea	Oligomenorrhea followed by amenorrhea	Oligomenorrhea
Duration of symptoms (months)	8	6	12
Body mass index	20.9	24.2	26.7
<i>Hormonal profile</i>			
Total testosterone (range 10–30 ng/dL)	591	679.96	490
DHEA-S (range 58–354 µg/dL)	145	312	179.9
17-OHP (range 0.18–2.3 ng/ml)	0.77	4.34	1.28
17-OHP 60 min after ACTH stimulation (< 10 ng/ml)		8.6	
<i>Imaging</i>			
Ultrasonography of abdomen and pelvis	Bulky left ovary (volume 50 cc)	Right ovarian hemorrhagic cyst 2.6 × 2.2 cm Polycystic ovarian disease	Hypoechoic lesion of 2.1 × 2.5 cm in right adnexa Decreased vascular resistance on Doppler
MRI (abdomen and pelvis)	No adrenal mass 3 × 4 cm T2 hyperintense solid–cystic mass in left ovary	No adrenal mass 3.6 × 3.2 × 2.6 cm complex mass in right ovary	No adrenal mass 2.6 × 2.8 cm solid mass in the right ovary
FDG-PET CT	–	Heterogenous FDG uptake in right bulky ovary	Hypermetabolic focus in bulky right ovary

DHEA-S Dehydroepiandrosterone sulfate, *17 OHP* 17 hydroxyprogesterone, *ACTH* adrenocorticotrophic hormone, *FDG-PET* fluorodeoxyglucose positron emission tomography

hormonal profile. Sudden onset and/or rapidly progressing hirsutism with signs of virilization usually points to a neoplastic etiology, either adrenal or ovarian. Grossly elevated serum testosterone levels, > 200 ng/dL along with a normal serum DHEA-S is highly suggestive of ovarian neoplasm, as DHEA-S is secreted solely by the adrenal glands. Determination of serum 17-OHP is important to rule out late-onset CAH, although the clinical features of this disorder are usually gradually progressive and less severe. In patients with raised 17-OHP, as was seen in Case 2, the diagnosis of CAH has to be confirmed by measuring the 17-OHP concentration 1 h after stimulation with intravenous ACTH. A value of < 10 ng/ml rules out late-onset CAH [1].

Ultrasonography is the initial imaging modality of choice. The sonographic appearance varies from small to large, solid to cystic masses, depending upon the histologic subtype. MRI provides further description of these tumors and provides additional information regarding presence or

absence of adrenal mass, lymphadenopathy and/or ascites [1].

The prognosis of these tumors depends upon surgical stage and histopathological characteristics. For SLCTs, both the stage and grade of tumor are important prognostic factors; well-differentiated tumors are almost always benign. Tumors at advanced stage, with poor or moderate differentiation and those with presence of heterologous elements (immature skeletal muscle or cartilage) on histopathology, are potentially malignant and are known to recur. For steroid cell tumors (NOS), the poor prognostic variables are: tumor size > 7 cm, ≥ 2 mitotic figures per high power field, necrosis, hemorrhage and grade 2 or 3 nuclear atypia. Leydig cell tumors are almost always benign; however, they do carry certain malignant potential that is yet to be determined [1–4].

Surgery is the mainstay of treatment for virilizing ovarian tumors. Due to rarity of bilateral disease and an early diagnosis, usually at stage 1, a fertility conserving surgery such as unilateral salpingo-oophorectomy with

Fig. 2 Enlarged right ovary in Case 2

careful staging is preferred in younger patients. Nowadays, laparoscopic approach is also acceptable. In older patients who have completed their family and those with advanced stage disease or presence of poor prognostic variables, a total abdominal hysterectomy with bilateral salpingo-oophorectomy with complete surgical staging is the treatment of choice. Role of postoperative chemotherapy for advanced stage tumors is still to be established. However, platinum-based adjuvant chemotherapy (BEP—bleomycin, etoposide, cisplatin) is frequently used for SLCTs and may be considered in steroid cell tumors (NOS). A careful follow-up is mandatory for all patients, especially in those who had conservative surgery. Recurrences are known to occur early after the first surgery, usually within 1 year [1–4].

Conclusion

Virilizing tumors of the ovary are rare causes of hyperandrogenism in women, affecting a wide range of age groups. Diagnosis is clinched by rapidly progressive symptoms and

elevated testosterone, aided by imaging techniques. Surgery is the mainstay of treatment, with the type and extent being affected by the age of the patient, desire for future fertility and stage of the tumor. A careful follow-up is essential to detect recurrences at the earliest.

Compliance with Ethical Standards

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

Ethical Approval All procedures followed were in accordance with the ethical standards of the Institutional Ethics Committee and with the Helsinki Declaration of 1975, as revised in 2008 (5).

Informed Consent Informed consent was obtained from all patients for being included in the study.

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