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A case of a virilising adult granulosa cell tumour

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Summary

Ovarian granulosa cell tumour (GCT) is recognized by two types: adult and juvenile. The diagnosis, treatment, and follow-up of a case of virilising adult GCT is reported.

Key words: Ovarian granulosa tumour; Virilisation.

Introduction

Ovarian granulosa cell tumours (GCTs) are rare malignant tumours of which two subtypes are recognised; adult and juvenile [1]. The former demonstrates a peak age frequency of 50-55 years and is more frequently associated with hyperandrogenism than the juvenile type [2]. The latter is seen in young adults and children and occurs in the first two decades of life [3], with less than five percent of these tumours occurring during premenarche [4].

Adult GCTs are the most common type of sex cord tumours, accounting for 1-2% of all ovarian tumours and 3% to 5% of ovarian malignancies [5]. Granulosa-theca cell tumours are the most common feminising tumour of the ovary [6] and are rarely associated with virilisation. Here the authors present a case of a female presenting with symptoms of hyperandrogenism secondary to a GCT.

Case Report

A 29-year-old G1P0 female presented with a four-year history of secondary amenorrhoea, severe acne, hair loss, hirsuitism, and secondary infertility. There was no report of anorexia, recent weight loss or other significant medical history. She was initially seen for worsening facial acne and blood tests at that time revealed an increased testosterone of 14.9 nmol/L (reference range 0-2.8 nmol/L) with a normal sex hormone binding globulin (SHGB) level of 33 nmol/L. Further review was conducted and clinical examination revealed normal blood pressure and body mass index. There was evidence of severe facial acne and acne on her upper chest and back. There was no facial hirsuitism, as she had commenced laser hair treatment one month prior to consultation. Hair stubble was evident over her abdomen and legs. The abdomen was mildly distended but there were no palpable masses and no clinical evidence of ascites.

Initial serum blood tests showed normal results for the following; dehydroepiandrosterone sulphate (DHEA-S) 5.7 micromol/L, 17-hydroxyprogesterone 9.4 nmol/L, follicle-stimulating hormone (FSH) 1.2 IU/L, luteinising hormone (LH) 14.8 IU/L, estradiol 138 pmol/L, progesterone 2.5 nmol/L, cortisol 413 nmol/L, prolactin 309 mIU/L, and thyroid stimulating hormone 1.7 mlU/L. A repeat testosterone remained elevated at 15.5 nmol/L.

Tumour markers were normal as follows: carbohydrate antigen-125 = 4KIU/L, alpha-fetoprotein 2.2 KIU/L, beta-hCG < 1I U/L, lactate dehydrogenase = 153 IU/L. Laboratory tests for inhibin A and inhibin B were not available.

Initial investigations of a contrast CT of the abdomen and pelvis showed a 73-mm low-density mass in the right adnexa, presumed ovarian in origin. The left ovary was not demonstrated and there was no associated adenopathy. The upper abdominal appearances were unremarkable and no adrenal lesions were identified. Following this, transvaginal ultrasound scan (TVUS) showed a well-defined heterogeneous right adnexal mass measuring 65×49×57mm that appeared solid in nature (Figures 1a and 1b). Doppler colour flow was present. The left ovary, uterus and endometrium appeared normal.

MRI of the pelvis and abdomen further demonstrated a predominantly solid lesion measuring 6.1×4.8×5.8 cm arising from the right ovary. The lesion was mainly homogenous with a few cystic areas within and showed heterogeneous enhancement with contrast. There was an intermediate signal on T1 and slightly hyperintense T2-weighted images. No pelvic or para-aortic lymphadenopathy, hydronephrosis or significant free fluid within the pelvis was noted.

The woman underwent laparoscopic excision of right fallopian tube and right ovary with retrieval of the intact specimen via a mini supra-pubic laparotomy. The ovary measured 85×58×40 mm and macroscopically the ovarian stroma was replaced by a solid tumour of ovary that measured 10 mm in diameter. There was no direct infiltration of the capsule.

Histology revealed a solid tumour characterised by diffuse cellular proliferation, which contained scant cytoplasm and round to oval nuclei. Luteinised cells were present, however there was no evidence of atypia or necrosis. Call-Exner bodies were present. The entire lesion was cellular, but found to have low mitotic index of ~4 mitosis/10 HPF. The stroma tumour exhibited strong inhibin expression as well as CD99 (focal) and calretinin (focal). The morphology and immunoprofile were those of a sex cord tumour consistent with an adult GCT. The patient subsequently resumed menstruation four weeks following surgery and clinically improved. Serum biochemistry demonstrated a normalisation of testosterone levels to < 0.7 nmol/L and remaining biochemistry was normal. Follow-up TVUS four weeks following surgery

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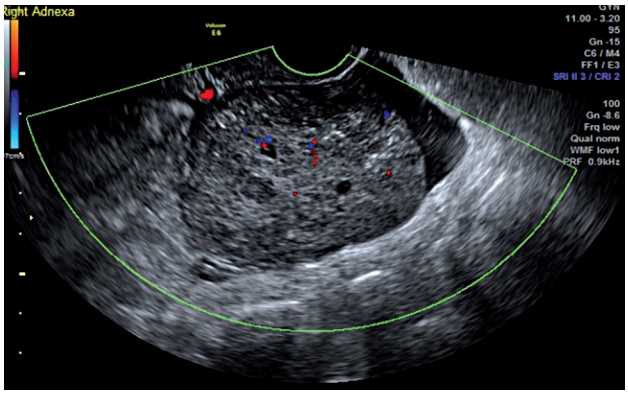

Figure 1. — a) Right adnexal heterogenous mass with colour Doppler flow present in TVUS.

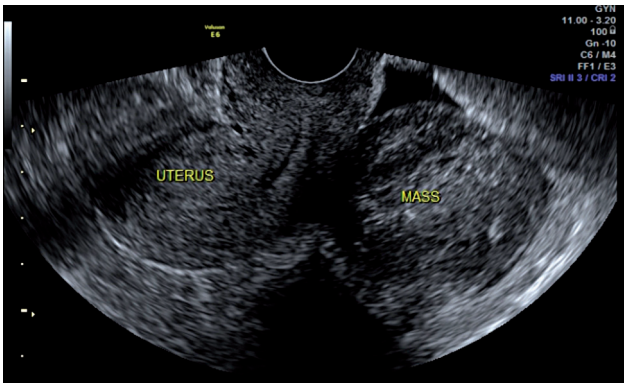

Figure 1. — b) Right adnexal mass with normal uterus adjacent on TVUS.

showed a normal appearance of the left ovary without adnexal masses or collections.

Following further multidisciplinary team discussion, it was recommended that the patient should undergo a repeat laparoscopy with staging, omentectomy, and omental biopsy four months following initial surgery. This was performed and histology obtained was negative for GCT. She subsequently became successfully pregnant one month later.

Discussion

Adult GCTs are the most common type of sex cord tumour and predominantly present with symptoms of hyperestrogenism including menstrual irregularities, menorrhagia and amenorrhoea, and are less associated with hyperandrogenism. Here the authors discuss adult type GCT and demonstrate a case where a female in her late 20s presented with symptoms of amenorrhoea and hyperandrogenism characterised by virilisation.

Androgenic manifestations reported in the literature include hirsuitism, clitorimegaly, a male escutcheon, deepening of the voice, temporal recession of the hairline, amenorrhoea, acne, and atrophy of the breasts [2]. Additionally, some cases have also presented with abdominal distension and an abdominal mass [7]. Theca cells of the ovarian stroma, which support the developing follicles, primarily produce androgens. Granulosa cells subsequently aromatise these into estrogens under the influence of FSH [2]. It has been observed that GCTs often exhibit the endocrine function and activity of normal granulosa cells, which include FSH binding and response to FSH, estrogen, testosterone, inhibin and progesterone activity, as well as Müllerian inhibiting substance secretion [8]. Hence, virilisation in a GCT has been noted as a paradoxical response due to this association with estrogen production [9]. This may be due to a number of reasons. It has been postulated that in such cases of GCTs with androgenic manifestations, the granulosa cells may lack aromatase to varying degrees. Therefore, estrogen conversion does not occur. It is suggested that pressure of the tumour cyst on granulosa cells could also potentially interfere with their aromatising ability to produce estrogens [2]. Furthermore, it has been documented that granulosa cells are capable of synthesising testosterone de novo [10], hence this may well contribute to some of the androgenic manifestations observed.

The testosterone produced has been shown to selectively inhibit FSH response to gonadotropin releasing hormone, hence why low levels of FSH may be observed [11]. This lack of FSH may further depress the aromatising potential of the granulosa cells.

Interestingly in children, estrogenic effects, such as pseudoprecocious puberty and irregular endometrial bleeding, also predominate in cases of GCTs [12]. However, research has shown that the unusual virilisation of girls with juvenile GCTs is related to a localised defect in aromatase expression in granulosa cells and ability of the interstitial cells to produce testosterone rather than dysregulation of SOX9 or FOXL2 (a virilising gene and ovary-determining gene respectively) [13].

Despite the mechanisms resulting in elevated serum testosterone, levels appear to normalise following excision of the tumour in the majority of cases. This response can be rapid and there have been reported cases where normalisation of testosterone levels has occurred within 24 hours following surgery [6, 14]. Often this has been accompanied by rapid regression of virilisation and improvement of clinical symptoms, as was seen in this reported case. Here the authors observed that there was a prompt return of menstruation following a four-year period of amenorrhoea followed by a desired pregnancy. Hence, the duration of elevated testosterone levels does not appear to have permanently interfered with the hypothalamo-pituitary ovarian axis or subsequent uterine function. Of note there have, however, been reports of a persistence of some symptoms including deepening of the voice and hirsuitism following tumour excision, but this appears to have occurred in a minority of cases [2].

Detection of GCTs using modern imaging modalities including ultrasonography can be challenging. The majority of virilising GCTs appear to be a solid mass and less com-

monly cystic or mixed masses [7]. Adult GCTs appear to be the most common GCT associated with virilisation [15], therefore clinical presentation must be considered in the differential diagnosis. The other tumour to consider is a mucinous cystic tumour if cystic appearances are observed on ultrasound. Presence of unilocular or multilocular thin-walled cystic neoplasm raises suspicion of a GCT [2].

Most GCTs present at an early FIGO Stage and the majority are unilateral. Five percent of GCTs have been documented as bilateral [16]. In the case of juvenile GCTs, the majority present at FIGO Stage I and confer a survival rate of 90% [17]. Treatment is mainly surgical with unilateral oophorectomy for those in which fertility is desired. Advanced stages and those with recurrent or metastatic disease may be treated with surgery and adjuvant cisplatin-based chemotherapy [12].

With regard to prognosis, few factors have been identified. There does not appear to be a correlation between tumour size or histology regarding prognosis [18]. The only identified factor that confirms poor prognosis is presence of extra-ovarian spread at initial diagnosis [19]. One-third of tumours show recurrence more than five years following initial treatment and one-fifth after ten years [18]. GCTs demonstrate a low mitotic index; therefore confer a more favourable prognosis. A reliable tumour marker needs to be identified to detect recurrence or new pathology. Inhibin A and B are glycoproteins produced by granulosa cells and used mainly in postmenopausal women as a marker of disease as levels are low. GCTs seem to demonstrate high levels of these proteins, therefore may be useful for recurrence detection following oophorectomy [20].

Conclusion

The authors presented the rare case of an adult GCT and highlighted the importance of considering such a diagnosis in women presenting with symptoms of hyperandrogenism. Although most tumours are detected at an early stage, prognosis remains undetermined, therefore long-term follow up is imperative.

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