Clinical Case Reports International

Case History
Published: 05 Oct, 2020

Androgenic Granulosa Cell Tumor in an Adolescent Female: An Unusual Presentation

*Supriya Dankher**

Department of Obstetrics and Gynecology, VMMC and Safdarjung Hospital, India

Abstract

In women, androgen secreting tumors can arise either from ovaries or adrenals. Virilizing ovarian tumors constitutes less than 0.2% of cases of hyper and rogenism and less than 1% of all ovarian tumors. Granulosa Cell Tumors (GCTs) usually produce estrogens, and hence, cause symptoms and signs of estrogen excess. GCT mostly present as perimenopausal and postmenopausal women with complaints of abnormal uterine bleeding. There are two distinct histological types, Adult GCT (AGCT) and Juvenile GCT (JGCT), which display different clinical and histopathological features. Adult Granulosa Cell Tumors (GCTs) are the most common type of ovarian sex cord tumors and account for 1% to 2% of all ovarian tumors. Juvenile granulosa cell tumor on the other hand is less common and occurs mainly in premenarchal girls.

We are reporting a case of an adolescent female presenting with features hyper and rogenism such as hirsutism, breast atrophy and clitoromegaly. On ultrasound, a cystic ovarian mass of 8.8 cm × 6.4 cm × 5.5 cm was seen in midline from which bilateral ovaries couldn't be demarcated. She underwent staging laparotomy followed by left salpingo-opherectomy which was histopathologically reported as adult granulosa cell tumor. Young age and androgen secreting nature of adult granulosa cell tumor make this case rare and worth reporting.

Introduction

Granulosa Cell Tumors (GCTs), adult type are the most common type of ovarian sex cord tumors and account for 1% to 2% of all ovarian tumors and 3% to 5% of all ovarian malignancies [1]. Granulosa cell tumors usually produce estrogens, and hence, cause symptoms and signs of estrogen excess. Endometrial hyperplasia was seen in 50% of the cases while adenocarcinoma uterus in 5% to 15% of the cases. GCT mostly present in perimenopausal and postmenopausal women with complaints of abnormal uterine bleeding [2].

Androgen secreting tumors in a female can arise from ovaries or adrenals. Among these, virilizing ovarian tumors constitutes less than 0.2% of cases of hyper androgenism [3] and less than 1% of all ovarian tumors [4]. Ovarian tumors that commonly present with hyper androgenism include Leydig cell tumors, Sertoli cell tumors, steroid cell tumors-not otherwise specified and ovarian the comas [5].

We are reporting a case of an adolescent female with features of hyper androgenism and ovarian mass which was histopathologically reported as adult granulosa cell tumor. Young age and androgen secreting nature of adult granulosa cell tumor make this case rare and worth reporting.

Case Presentation

A 16 years old unmarried female reported to our Gynae OPD with complaints of delayed and scanty periods and hirsutism over last 2 years, followed by secondary amenorrhea for last 6 months. She attained her menarche at 12 years of age and her previous menstrual cycles were normal with regular flow. On examination, signs of verification such as breast atrophy (Tanner stage 2), hirsutism and clitoromegaly were present. Per abdominal examination was normal. On per rectal examination, an ill defined mass was felt in midline of approximately 5 cm × 4 cm, cystic, non-tender and freely mobile. The patient's vital parameters and other physical findings were normal.

On USG, a large lobulated septated cystic mass of 8.8 cm × 6.4 cm × 5.5 cm was seen in midline in lower abdomen with bilateral ovaries couldn't be seen separately. Rest of abdomen viscera and bilateral kidneys and adrenals were within normal limits. On MRI, USG findings were corroborated, bilateral ovaries can't be seen separately and bilateral adrenals and uterus were normal. On, lab

OPEN ACCESS

Correspondence:
Supriya Dankher, Department of Obstetrics and Gynecology, VMMC and Safdarjung Hospital, India, Tel: +91-8505813686;
E-mail: supsdhankher@gmail.com

Received Date: *08 Sep 2020*
Accepted Date: *01 Oct 2020*
Published Date: *05 Oct 2020*

Citation:
Dankher S. Androgenic Granulosa Cell Tumor in an Adolescent Female: An Unusual Presentation. Clin Case Rep Int. 2020; 4: 1186.

Copyright *© 2020 Supriya Dankher. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.*

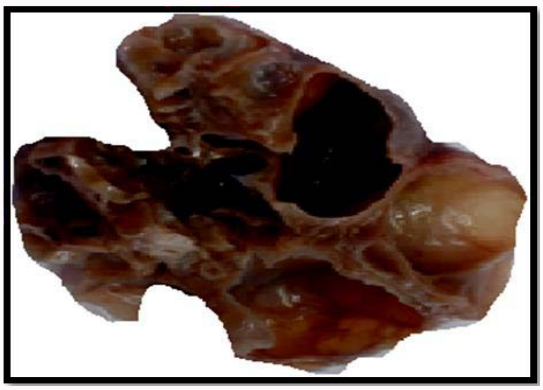

Figure 1: Gross Solid-cystic appearance of left ovarian tumor.

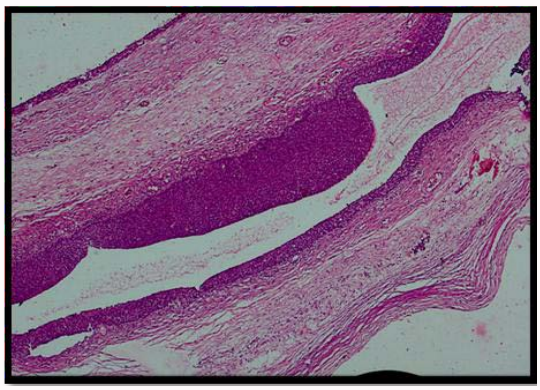

Figure 2: Microscopic appearance of left ovarian tumor.

investigations, serum DHEAS (607) & S. testosterone (156.31) were markedly raised while serum FSH, LH and other tumor markers (CA 125, alpha FP, S. beta HCG, S. LDH) were WNL. There was no significant family history of malignancy. She was planned for staging laparotomy with a provisional diagnosis of androgen secreting ovarian sex cord stromal tumor. On laparotomy, no gross ascites or peritoneal or omental deposits were present. Peritoneal wash fluid sent for cytology. Uterus, right ovary and right fallopian tube were WNL while a left ovarian multiloculated cyst of 4 cm × 6 cm was seen with intact capsule. Left fallopian tube was also WNL. Left salpingo-opherectomy was done and was sent for HPE.

On histopathological examination, to our surprise, this was reported as adult type granulosa cell tumor Stage IA1 with presence of typical Call - Exner bodies and coffee bean shaped nucleus. Serum inhibin levels done after HPE, one week postoperatively were normal. This diagnosis of androgen secreting variety of a commonly known estrogen secreting tumor, lead us to undergo literature search and publish this unusual presentation (Figure 1). Patient resumed her menses in very next cycle of surgery and her virilizing and hirsute features got resolved, other than clitoromegaly, during her follow up examination at 3 months. She have no complaints for last one year of follow up and is on regular follow up with USG and serum testosterone and DHEAS levels (Figure 2).

Discussion

Granulosa Cell Tumors (GCT) is derived from the granulosa cells of ovary. They constitute less than 5% of all ovarian tumors and more than 70% of the sex cord-stromal tumors. There are two distinct histological types - Adult GCT (AGCT) and Juvenile GCT (JGCT), which display different clinical and histopathological features. AGCTs are more common (95%) and are usually seen in perimenopausal and postmenopausal women. JGCTs are rare tumors, representing 5% of all GCTs and usually occur in premenarchal girls and young women [6]. On microscopic examination, two characteristics distinguish juvenile from adult granulosa cell tumors: The nuclei of juvenile granulosa cell tumors are rounded, hyper chromatic and un-grooved with moderate to abundant eosinophilic or vacuolated cytoplasm, and the theca cell component is luteinized [6].

The majority of patients with GCT will present with one or a combination of the following clinical symptoms: Abnormal vaginal bleeding, abdominal distention, and abdominal pain. Other clinical manifestations are breast tenderness, uterine myo-hypertrophy, and endometrial hyperplasia. All these are consistent with an estrogen-secreting tumor. The endocrine function of GCTs, specifically the production of estrogens, has been repeatedly demonstrated by assessment of the end organ i.e., endometrium, and measurements of peripheral levels of estrogen before and after surgery. Also, there are studies where selective ovarian venous catheterizations during surgery have the secretion of large quantities of estrogen from the ovary harboring the GCT [7]. On molecular level, *FOXL2* gene is required for the normal development of the granulosa cell and mutation of *FOXL2* seen in 97 % of adult GCT and is considered as pathognomonic for GCT (particularly adult GCT) [6]. This mutation leads to unregulated aromatase action and excessive estrogen production by action of aromatase on androstenedione in GCTs.

GCTs are low potential malignant neoplasms with the capacity for local or lymphatic extension, particularly to the para-aortic lymph nodes. As GCTs usually detectable in early stages due to features of hyper estrogenism, unilateral oophorectomy is recommended treatment for women who wish to preserve their fertility. However, GCT has a tendency for late recurrence and once the tumor recurs it's fatal in 80% cases [6]. Therefore, it is important to have a circulating marker as an early predictor or recurrent disease.

Estrogens are generally produced by GCTs, but role of estrogens as a tumor marker is limited, as no correlation between serum estrogen levels and tumor load was noted [6].

Other tumor markers being considered for GCT are Inhibin B and MIS. In the postmenopausal women, with depletion of ovarian follicles, inhibin levels become undetectable. But in GCT, inhibin (predominantly inhibin B) is secreted by granulosa cells, thus inhibin B can be used as a marker for GCT in premenopausal and postmenopausal women. Inhibin act as autocrine and paracrine granulosa cell growth factors and hence, levels of inhibin reflect the tumor burden. However, not all GCTs express inhibin [6] and epithelial ovarian tumors especially the mucinous variety may also secrete inhibin (82% cases) suggesting that inhibin is not specific for GCT [6]. MIS is also formed in granulosa cells during reproductive life and parallels changes in inhibin levels in GCT. Also, an elevated level of MIS is highly specific for GCT [6].

Occasionally, patients with GCTs also presents with decidual reaction of the stroma or secretory characteristics of the glands in endometrium which consistent with tumor production of progesterone. Rarely, virilizing changes as primary or secondary amenorrhea, hirsutism, and clitoral hypertrophy, deepening of the voice, masculine features and acne due to elevated testosterone levels

are seen in GCTs [7].

Androgen secreting adult type GCT is a rare tumor in young females but was do reported over years. Castro et al. [8] reported first case androgenic adult GCT in a prepubertal female presented with hirsutism, raised serum testosterone and 17-hydroxyprogesterone levels. Unilateral salpingo-opherectomy was done and histopathology showed findings suggesting adult type GCT. A reported case of Juvenile GCT, with androgenic manifestations in a 13-year-old girl was also found. Juvenile GCT is as such less common and usually manifest estrogenic features. Her plasma testosterone level was elevated and pelvic ultrasonography revealed a left adnexal cyst (14.4 cm × 9.1 cm × 9.7 cm). The patient underwent an exploratory laparotomy, revealing a left ovarian cystic tumor reported as juvenile granulosa cell tumor on histopathology [9].

Although, androgen secreting GCT are similar to estrogen secreting GCTs in histopathology, it is suggested that they may have a sertoli-leydig cell component which can cause androgen secretion in these women [6]. Another hypothesis is based on the two-cell hypothesis of estradiol production i.e. granulosa cells produce estradiol if the precursor testosterone is secreted by adjacent theca cells. However, in androgenic granulosa cell tumors, few theca cells and lack of aromatase activity of varying degrees in granulosa cells, were seen, leading to accumulation of androgens as they can't be converted to estradiol [9].

Although, Inhibin B is commonly used as tumor markers for GCT but Inhibin B levels were normal in above mentioned cases including our case. While serum testosterone and DHEAS levels were raised in all of these cases, but use of these as tumor markers is still a matter to be subjected for further research. Other serum biochemical markers were also reported to be raised in androgenic GCTs by some authors.

Niwa et al. [10] reported a 32-year-old Japanese woman, with signs of virilization & pelvic mass on USG with raised serum LH, serum testosterone and DHEAS levels. She underwent laparoscopic right salpingo-opherectomy and the tumor was diagnosed as an adult-type GCT. The reason for the elevation of LH levels in this case was not clear but serum LH levels falls to normal range after surgery. Authors proposed the role serum LH levels in such females for follow up [10].

Honda et al. [11] reported another rare case of androgenic adult GCT in a 29 year old female presenting with secondary amenorrhea and adnexal mass and no other signs of virilization. On investigation serum testosterone levels and aPTT were raised which returned to normal levels after surgery. Authors proposed role of an inhibitor to an APTT-based clotting factor being produced by tumor causing raised APTT.

Conclusion

Authors conclude that preoperative diagnosis of androgenic GCT is not feasible and histopathology remains the gold standard. But, a possibility of androgenic GCT should be considered in women with virilizing features and ovarian mass. During follow up of these cases, serum biochemical markers which were raised preoperatively such as serum testosterone & DHEAS in present case along with established tumor marker for GCT i.e., serum inhibin B levels, in addition to clinical examination and pelvic imaging at regular intervals, should be done. Further research and need of analysis of existing literature is required on time to time basis in order to suggest relevant tumor markers, follow up and prognosis in these cases.

References

1. Young RH, Scully RE. Endocrine tumors of the ovary. Curr Top Pathol. 1992;85:113-64.
2. Takemori M, Nishimura R, Hasegawa K. Ovarian thecoma with ascites and high serum levels of CA 125. Arch Gynecol Obstet. 2000;264(1):42-4.
3. Cohen I, Nabriski D, Fishman A. Noninvasive test for the diagnosis of ovarian hormone-secreting-neoplasm in postmenopausal women. Gynecol Oncol Rep. 2016;15:12-5.
4. Burnik Papler T, Frković Grazio S, Kobal B. Sertoli - Leydig cell tumor with retiform areas and overgrowth of rhabdomyosarcomatous elements: Case report and literature review. J Ovarian Res. 2016;9(1):46.
5. Park JW, Bae JW. Postmenopausal Meigs' Syndrome in Elevated CA-125: A Case Report. J Menopausal Med. 2015;21(1):56-9.
6. Kottarathil VD, Antony MA, Nair IR, Pavithran K. Recent advances in granulosa cell tumor ovary: A review. Indian J Surg Oncol. 2013;4(1):37-47.
7. Gershemson DM, Dowdy SC, Young RH. Ovarian sex cord stromal tumors. In: Principles and practice of gynaecologic oncology. Barakat RR, Berchuck A, Markman M, Randall ME, editors. Phildelphia: Lippincott Williams & Wilkins. 2013. p. 866-85.
8. Castro CY, Malpica A, Hearne RH, Silva EG. Androgenic adult granulosa cell tumor in a 13 year old prepubertal patient: A case report and review of literature. Int J Gynecol Pathol. 2000;19(3):266-71.
9. Nomelini RS, Micheletti AM, Adad SJ, Murta EF. Androgenic juvenile granulosa cell tumor of the ovary with cystic presentation: A case report. Eur J Gynaecol Oncol. 2007;28(3):236-8.
10. Niwa K, Yano R, Mori S, Yamaguchi Y, Narikawa N, Tanaka T. Androgenic adult granulosa cell tumorwith secondary amenorrhea and elevated luteinizing hormone. Pathol Discov. 2013;1:9.
11. Honda T, Fukasawa H, Hashi A, Minai M, Hirata S, Hoshi K. Androgenic adult granulosa cell tumor with prolongation of the activated partial thromboplastin time in a 29 year old woman. BJOG. 2003;110(4):433-5.