Volume 4 Issue 1
March 2023
SLJOM The Sri Lanka Journal of Menopause

Case Report

A Case Report on Adult Granulosa Cell Tumour of the Ovary with Atypical Endometrial Hyperplasia: A Diagnostic & Management Conundrum.

Hewawitharana KG[1], Meegoda VJ[1], Jayawardane M[1], Nimana KVH[1], Fereen WFN[1], Chandrasena UGSD[1]

[1] *Professorial Unit, Colombo South Teaching Hospital, Kalubowila, Sri Lanka*

Corresponding author – Hewawitharana KG - Email-kavi88fmas@gmail.com

Abstract

Adult granulosa cell tumours of the ovary are rare malignancies with good prognoses and a tendency for late recurrences. Manifestations of unopposed estrogen are common with various degrees of endometrial hyperplasia. Surgery remains the mainstay of treatment and the effectiveness of adjuvant therapy still remains to be seen. The usefulness of tumour markers for follow-up is yet to be proven but prolonged surveillance is mandatory as recurrences occur years following initial surgery.

Keywords: Adult granulosa cell tumour, Ovarian malignancy, Endometrial hyperplasia

Background

Adult granulosa cell tumour (AGCT) of the ovary is an uncommon neoplasm representing 2 - 3% of all ovarian malignancies, with an incidence of less than 3.7 per 100,000 women[1,2,3,4]. They occur in the peri and early postmenopausal period with peak prevalence in patients aged 50 to 55 years. The uncommon juvenile GCT peaks around the pre-pubertal age[2,3,5]. The adult form progresses slowly and often is diagnosed in an early stage of the disease and has excellent survival outcomes[2]. Surgery is the primary treatment for ovarian AGCT. Patients with advanced and recurrent disease can be given adjuvant therapy, including radiotherapy, chemotherapy, hormonal and targeted therapy[3]. Recurrences that occur years later, can affect the prognosis.

Sri Lanka has minimal recorded data on AGCT, but population studies show a clear increase in ovarian cancers over the last few years[6,7,8,9]. Despite its rarity, a proper management sequence and guidelines need to be established at the local level as early diagnosis and proper treatment can lead to excellent outcomes.

Case Presentation

A 51-year-old multipara with a background history of diabetes mellitus presented with irregular heavy menstrual bleeding for four months duration. On gynaecological examination uterus was normal in size, the cervix appears normal and no adnexa masses were noted. The Transvaginal scan revealed a thick endometrium of 15mm, with ultrasonically normal-looking ovaries on both sides with no evidence of free fluid.

The patient underwent hysteroscopy which showed multiple small polyps in the endometrial cavity and was subjected to dilatation & curettage. Histology revealed atypical endometrial hyperplasia. As the patient had completed her family, a total abdominal hysterectomy and bilateral salpingo-oophorectomy were carried out. Histology of the final specimen revealed atypical endometrial hyperplasia with adult granulosa cell tumour of the ovary (AGCT). These findings were quite unexpected as ultrasound and gross morphology did not reveal evidence of an ovarian neoplasm and she did not have apparent risk factors either. Further management plan of the patient included specialized multi-disciplinary team

involvement, contrast CT of the abdomen-pelvis and completion of omentectomy.

Discussion

AGCT is a unique type of ovarian cancer with a good prognosis and a tendency towards a late recurrence. AGCT originates from proliferating normal preovulatory granulosa cells (GCs) and retains several features of those GCs[3]. Compared to more common epithelial ovarian cancers, GCTs have different biology and clinical presentation due to their retained ability to produce estrogen, which leads to abnormalities in menstruation and early presentation; as such, these tumours are detected 80-90% of the time in stage I, thus leading to favorable outcomes[10,11,12]. Common symptoms include abdominal pain, abdominal distension due to mass effect and hormonal events including irregular menstruation, intermenstrual bleeding, postmenopausal bleeding or amenorrhea, while around 20% remain asymptomatic[1,2,12].

Patients often have an abnormal endometrium due to long-term exposure to endogenous, abnormal estrogen. Approximately one-third of the patients present with endometrial hyperplasia and around 2% of the patients are diagnosed with concurrent endometrial cancer[1,3,13,14]. Biopsy remains standard practice and mostly turns out to be normal endometrium[13].

AGCT shows significant variations in size, ranging from small invisible lesions to huge masses with a range of 1 to 30 cm, with an average diameter of around 10 cm. Radiologically they are usually seen as a solid mass with a multi-cystic appearance[2,3,6,15]. As in our patient ovarian masses are not always visible and diagnosis can be easily missed if not evaluated methodically.

Specific tumour markers are crucial for accurate early diagnosis and postoperative follow-up to detect recurrences early. The hormonal activity of ovarian AGCT suggests that these hormones can be used as tumour markers[3]. The serum level of CA-125, estradiol, inhibin, and anti-Müllerian hormone, are used in different capacities but none has been correlated with tumour progression in large studies[17,18].

A study conducted in 2009 reported that approximately 97% of the cases of AGCT had somatic missense mutations in the transcription factor FOXL2[16]. Subsequent studies proved that the mutation does not exist in other cancers, including JGCTs and this is pathognomonic for AGCTs[19,20,21]. The FOXL2 mutation provides theoretical support for the clinical diagnosis, exploration of the pathogenesis and treatment of AGCT. Nonetheless, the pathogenesis remains unclear and despite extensive exploration, targeted treatment is still under development[2,3].

The evidence-based management of AGCT is limited considering the rarity of the condition. Surgery remains the mainstay of treatment for primary and recurrent AGCT, and there is no other effective treatment[3,24]. Total abdominal hysterectomy and bilateral salpingo-oophorectomy remain the standard in primary AGCT and debulking surgery for advanced-stage or recurrent disease[1,25,26]. Surgery can be performed by either laparotomy or laparoscopy and studies have reported that laparoscopic surgery has high safety and a low recurrence rate[27]. Generally, pelvic and para-aortic lymph node resection is not recommended, and only large or suspected lymph nodes are removed during the surgery[26]. Our patient's pattern of presentation signifies the need to consider oophorectomy in a patient with atypical endometrial hyperplasia.

Currently, there are no standard international guidelines and the

International Federation of Gynecology and Obstetrics (FIGO) staging system is applied routinely[28]. The stage during primary surgery is crucial for the prognosis of the patients[2]. The majority of patients with ovarian AGCT present with stage IA disease, with tumours commonly being confined to the ovary without metastasis[29]. Relatively low incidence and late recurrence of AGCT and lack of prospective randomized trials leads to difficulty in forming a consensus on adjuvant therapy[32,33]. In addition, there is no evidence that postoperative adjuvant chemotherapy prevents recurrence[34,35]. Schumer and Cannistra[29] reported that use of adjuvant chemotherapy and radiation therapy have sometimes been associated with prolonged disease-free survival in high-risk patients with advanced stages & unresectable tumour.

Radiotherapy has been proposed and tested for recurrent disease, postoperative residual disease, and palliative treatment[13,36]. In addition, hormone therapy is recommended for patients who do not respond or develop resistance to conventional chemotherapy. Treatment options that have been explored include, the use of GnRH agonists, aromatase inhibitors and tamoxifen (selective estrogen receptor modulator)[2,3,26]. The current chemotherapy, radiotherapy & targeted hormone therapy regimens have not yielded satisfactory results and therefore it is necessary to develop alternative therapies which are more selective with less side effects to treat patients who are unable undergo surgery[2,3,37].

In comparison to epithelial ovarian cancers, AGCT are characterized by good prognosis[3,17,29,38,39]. The overall 5-year survival and 9-year survival rates for all stages were 91.3% and 77.3%, respectively[1]. There has been some controversy in the detection of prognostic factors; however, the stage of the tumour is accepted as the most important prognostic factor and strongest predictor of recurrences in most studies[13,36,37]. The five-year disease-free survival rates were 92% for stage I, 89% for stage II, and 50% for stage III (2).

No proper consensus had been reached regarding other prognostic factors. Large tumour size (>10cm), older age at initial diagnosis (>40 years)1], residual disease following initial surgery, association with p53 mutation, number of mitoses on biopsy are considered to be associated with poor prognosis, but these have not been confirmed with large scale trials[1,2,11,17,34,38,40,41,42,43]. Ascites, positive cytology, bilateral disease, capsule invasion, tumour rupture, fertility preserving surgery have not been identified as contributors for poor prognosis or recurrence[2,29,43].

The evolution of AGCT is slow and recurrences are rare and often delayed[38]. Studies have shown that at least one third of the patients will experience a relapse following a prolonged disease-free period ranging from 6 to 23 years and at least half of them will succumb to disease following the recurrence[3,36]. The most common site for recurrence is in the pelvis[27,32]. In a multicenter retrospective study in Korea, advanced stage was identified as the only factor related to increased recurrences[2]. Even though CA-125 is considered as the primary indicator of epithelial ovarian cancer recurrence, its relevance as a marker in AGCT is controversial[37,44]. The serum markers inhibin, anti-Mullerian hormone and estradiol can be used for the early diagnosis and postoperative follow-up of patients with AGCT. However, studies have reported biases; therefore, the detection of serum markers alone is not adequate to diagnose[3,45-48]. Routine follow up should include careful gynecological examination and use of above-mentioned serum markers[3]. Debulking surgery, when feasible, remains the most effective treatment for recurrent ovarian AGCT[2].

Conclusion

AGCT of the ovary is an uncommon neoplasm with favourable prognosis and late recurrences. Stage is the only factor associated with disease-free survival. Surgery remains the mainstay of management and fertility-sparing surgery may be a treatment option for women with early-stage disease who wishes to retain fertility. Due to the rarity of this disease, further prospective studies are needed to establish a consensus in management & follow up.

References

1. Sekkate S, Kairouani M, Serji B, Tazi A, Mrabti H, Boutayeb S, et al. Ovarian granulosa cell tumors: A retrospective study of 27 cases and a review of the literature. World J Surg Oncol. 2013;11:1–6.
2. Lee IH, Choi CH, Hong DG, Song JY, Kim YJ, Kim KT, et al. Clinicopathologic characteristics of granulosa cell tumors of the ovary: A multicenter retrospective study. J Gynecol Oncol. 2011;22(3):188–95.
3. Li X, Tian B, Liu M, Miao C, Wang D. Adult-type granulosa cell tumor of the ovary. Am J Cancer Res [Internet]. 2022;12(8):3495–511. Available from: www.ajcr.us/
4. Granulosa Cell Tumors of the Ovary - Prognosis and Outcome.
5. Stenwig JT, Hazekamp JT, Beecham JB. Granulosa cell tumors of the ovary. A clinicopathological study of 118 cases with long-term follow-up. Gynecol Oncol. 1979;7(2):136–52.
6. Alpitiarachchi N, Kariyawasam CJ, Perera S, Munas M. An insight into ovarian cancer incidence trends in Sri Lanka, 2005-2019. J Coll Community Physicians Sri Lanka. 2022;27(5):125.
7. Vithana PVSC, Dheerasinghe DSA., Handagiripathira HMI, Alahapperuma S, Nilaweera I, Perera S. Sri Lankan Patterns of Female Cancers: Incidence and Mortality Over 1995-2010. Asian Pacific J Cancer Care. 2021;6(1):27–33.
8. De Silva RS, Dinusha AK, Kottegoda GJDE, Kannangara DE, Premaratne S. Patients with ovarian cancer – knowledge and awareness of their disease, treatment, and possible complications. Sri Lanka J Obstet Gynaecol. 2021;43(4):278.
9. Thirukumar M, Sinnathurai A. Gynaecological Malignancies Among a Representative Population of Batticaloa, Sri Lanka. Cureus. 2021;13(1):1–7.
10. McNatty KP, Makris A, Degrazia C, Osathanondh R, Ryan KJ. The production of progesterone, androgens, and estrogens by granulosa cells, thecal tissue, and stromal tissue from human ovaries in vitro. J Clin Endocrinol Metab. 1979;49(5):687–99.
11. Study C, Of C, Cell G, Reference S, Prognosis FI. A of 92. 1973;
12. Segal R, DePetrillo AD, Thomas G. Clinical review of adult granulosa cell tumors of the ovary. Vol. 56, Gynecologic Oncology. 1995. p. 338–44.
13. Chou CF, Huang WC. Granulosa cell tumor of the ovary. Tzu Chi Med J. 2016;28(2):84–5.
14. Pautier P, Lhommé C, Culine S, Duvillard P, Michel G, Bidart JM, et al. Adult granulosa-cell tumor of the ovary: A retrospective study of 45 cases. Int J Gynecol Cancer. 1997;7(1):58–65.
15. Stuart GCE, Dawson LM. Update on granulosa cell tumours of the ovary. Curr Opin Obstet Gynecol. 2003;15(1):33–7.
16. Wang WC, Lai YC. Molecular pathogenesis in granulosa cell tumor is not only due to somatic FOXL2 mutation. J Ovarian Res. 2014;7(1):1–5.
17. Ayhan A, Salman MC, Velipasaoglu M, Sakinci M, Yuce K. Prognostic factors in adult granulosa cell tumors of the ovary: A retrospective analysis

of 80 cases. J Gynecol Oncol. 2009;20(3):158–63.
18. Nejm198909213211204. 2010;
19. Jamieson S, Butzow R, Andersson N, Alexiadis M, Unkila-Kallio L, Heikinheimo M, et al. The FOXL2 C134W mutation is characteristic of adult granulosa cell tumors of the ovary. Mod Pathol. 2010;23(11):1477–85.
20. Kim MS, Hur SY, Yoo NJ, Lee SH. Mutational analysis of FOXL2 codon 134 in granulosa cell tumour of ovary and other human cancers. J Pathol. 2010;221(2):147–52.
21. Al-Agha OM, Huwait HF, Chow C, Yang W, Senz J, Kalloger SE, et al. FOXL2 is a sensitive and specific marker for sex cord-stromal tumors of the ovary. Am J Surg Pathol. 2011;35(4):484–94.
22. Gershon R, Aviel-Ronen S, Korach J, Daniel-Carmi V, Avivi C, Bar-Ilan D, et al. FOXL2 C402G mutation detection using MALDI-TOF-MS in DNA extracted from Israeli granulosa cell tumors. Gynecol Oncol [Internet]. 2011;122(3):580–4. Available from: http://dx.doi.org/10.1016/j.ygyno.2011.05.008
23. McConechy MK, Farkkila A, Horlings HM, Talhouk A, Unkila-Kallio L, Van Meurs HS, et al. Molecularly defined adult granulosa cell tumor of the ovary: The clinical phenotype. J Natl Cancer Inst. 2016;108(11):1–5.
24. Leung DTH, Fuller PJ, Chu S. Impact of FOXL2 mutations on signaling in ovarian granulosa cell tumors. Int J Biochem Cell Biol [Internet]. 2016;72:51–4. Available from: http://dx.doi.org/10.1016/j.biocel.2016.01.003
25. Ray-Coquard I, Morice P, Lorusso D, Prat J, Oaknin A, Pautier P, et al. Non-epithelial ovarian cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol [Internet]. 2018;29(April):iv1–18. Available from: https://doi.org/10.1093/annonc/mdy001
26. Colombo N, Parma G, Zanagnolo V, Insinga A. Management of ovarian stromal cell tumors. J Clin Oncol. 2007;25(20):2944–51.
27. Fotopoulou C, Savvatis K, Braicu EI, Brink-Spalink V, Darb-Esfahani S, Lichtenegger W, et al. Adult granulosa cell tumors of the ovary: Tumor dissemination pattern at primary and recurrent situation, surgical outcome. Gynecol Oncol [Internet]. 2010;119(2):285–90. Available from: http://dx.doi.org/10.1016/j.ygyno.2010.06.031
28. Bryk S, Färkkilä A, Bützow R, Leminen A, Heikinheimo M, Anttonen M, et al. Clinical characteristics and survival of patients with an adult-type ovarian granulosa cell tumor a 56-year single-center experience. Int J Gynecol Cancer. 2015;25(1):33–41.
29. Schumer ST, Cannistra SA. Granulosa cell tumor of the ovary. J Clin Oncol. 2003;21(6):1180–9.
30. Färkkilä A, Haltia UM, Tapper J, McConechy MK, Huntsman DG, Heikinheimo M. Pathogenesis and treatment of adult-type granulosa cell tumor of the ovary. Ann Med. 2017;49(5):435–47.
31. GUBERN SALISACHS L, MARQUES GUBERN A. Tumors of the ovary. Acta pediátrica española. 1961;19:377–92.
32. 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.
33. Jamieson S, Fuller PJ. Management of granulosa cell tumour of the ovary. Curr Opin Oncol. 2008;20(5):560–4.
34. Al-Badawi IA, Brasher PMA, Ghatage P, Nation JG, Schepansky A, Stuart GCE. Postoperative chemotherapy in advanced ovarian granulosa cell tumors. Int J Gynecol Cancer.

2002;12(1):119–23.
35. Uygun K, Aydiner A, Saip P, Kocak Z, Basaran M, Dincer M, et al. Clinical parameters and treatment results in recurrent granulosa cell tumor of the ovary. Gynecol Oncol. 2003;88(3):400–3.
36. Pectasides D, Pectasides E, Psyrri A. Granulosa cell tumor of the ovary. Cancer Treat Rev. 2008;34(1):1–12.
37. Tak JY, Chong GO, Park JY, Lee SJ, Lee YH, Hong DG. Adult granulosa cell tumor presenting with massive ascites, elevated CA-125 level, and low 18 F-fluorodeoxyglucose uptake on positron emission tomography/computed tomography . Obstet Gynecol Sci. 2015;58(5):423.
38. Li W, Wu X, Fang CQ, Yao JF, Guo Y, Zhang SL. Prognostic factors in adult granulosa cell tumor of the ovary. Saudi Med J. 2009;30(2):247–52.
39. Miller K, McCluggage WG. Prognostic factors in ovarian adult granulosa cell tumour. J Clin Pathol. 2008;61(8):881–4.
40. Chan JK, Zhang M, Kaleb V, Loizzi V, Benjamin J, Vasilev S, et al. Prognostic factors responsible for survival in sex cord stromal tumors of the ovary - A multivariate analysis. Gynecol Oncol. 2005;96(1):204–9.
41. pubmed.ncbi.nlm.nih.gov [Internet]. Available from: https://pubmed.ncbi.nlm.nih.gov/15154651/
42. Ala-Fossi SL, Mäenpää J, Aine R, Koivisto P, Koivisto AM, Punnonen R. Prognostic significance of p53 expression in ovarian granulosa cell tumors. Gynecol Oncol. 1997;66(3):475–9.
43. Factors in Granulosa-Cell. 1981;274:261–74.
44. Timmerman D, Moerman P, Vergote I. Meigs' syndrome with elevated serum CA 125 levels: Two case reports and review of the literature. Gynecol Oncol. 1995;59(3):405–8.
45. Geerts I, Vergote I, Neven P, Billen J. The role of inhibins B and antimüllerian hormone for diagnosis and follow-up of granulosa cell tumors. Int J Gynecol Cancer. 2009;19(5):847–5
46. Färkkilä A, Koskela S, Bryk S, Alfthan H, Bützow R, Leminen A, et al. The clinical utility of serum anti-Müllerian hormone in the follow-up of ovarian adult-type granulosa cell tumors - A comparative study with inhibin B. Int J Cancer. 2015;137(7):1661–71.
47. Manuscript A. or Radiology. 2010;114(1):57–60.
48. Rey RA, Lhomme C, Marcillac I, Lahlou N, Duvillard P, Jesse N, et al. Antimullerian hormone as a serum marker of granulosa cell tumors of the ovary: Comparative study with serum α-inhibin and estradiol. Am J Obstet Gynecol. 1996;174(3):958–65.