



Case Report

A Case Report on Adult Granulosa Cell Tumour of the Ovary with Atypical Endometrial Hyperplasia: A Diagnostic & Management Conundrum.**Hewawitharana KG¹, Meegoda VJ¹, Jayawardane M¹, Nimana KVH¹, Fereen WFN¹, Chandrasena UGSD¹**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 outcomes². 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

therapy³. 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 GCs³. 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 endometrium¹³.

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 markers³. 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 FOXL2¹⁶. 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 rate²⁷. Generally, pelvic and para-aortic lymph node resection is not recommended, and only large or suspected lymph nodes are removed during the surgery²⁶. 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 routinely²⁸. The stage during primary surgery is crucial for the prognosis of the patients². The majority of patients with ovarian AGCT present with stage IA disease, with tumours commonly being confined to the ovary without metastasis²⁹. 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 Cannistra²⁹ 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%, respectively¹. 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 delayed³⁸. 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 recurrences². 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 markers³. Debulking surgery, when feasible, remains the most effective treatment for recurrent ovarian AGCT².



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.

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