

## Adult Granulosa Cell Tumour of the Ovary Associated with Endometrial Carcinoma in a Postmenopausal Woman: A Case Report.

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**Abstract:** Granulosa Cell Tumours (GCTs) of the ovary are rare and account for 2-5% of all ovarian cancers. They are divided into juvenile and adult types. Adult types constitute 95% of all GCTs. GCTs secrete large amounts of sex steroids such as estrogen. Prolonged elaboration of high levels of estrogen by adult GCTs may be associated with proliferative breast disease, endometrial hyperplasia and rarely endometrial carcinoma (EC). We report a case of 59 year old woman referred to our hospital on account of 3-month history of vaginal bleeding with 18-day history of abdominal swelling and pains. Histopathologic evaluation of surgical biopsies obtained from her confirmed ovarian GCT with extensive omental and peritoneal spread and associated Grade 2 endometrioid adenocarcinoma. The rarity of this association and the unique pattern of this case are highlighted to stimulate a high index of suspicion for such among clinicians in our environment.

**Keywords:** Adult, Endometrial Carcinoma, GCT (Granulosa Cell Tumour), Ovarian

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### I. Introduction

GCT is a rare type of neoplasm arising from the ovarian sex cord-stromal cells and accounts for 2 – 5% of all ovarian cancers<sup>[1,2,3]</sup>. It presents most commonly with abnormal vaginal bleeding before, during or after menopause and is characterized by prolonged natural history and a tendency to late reoccurrence<sup>[4,5,6]</sup>. Based on their clinical and histopathological studies, GCTs are classified into juvenile and adult types<sup>[7]</sup>. Nearly all GCTs are capable of secreting large amounts of estrogen<sup>[7,11]</sup>. This main characteristic of GCTs is responsible for iso-sexual precocious pseudopuberty in young girls with the juvenile type<sup>[11,12]</sup>. In adults, prolonged exposure to high estrogen levels in functionally active GCTs may be associated with proliferative breast disease, endometrial hyperplasia and EC<sup>[1,4,11]</sup>. Reports of GCTs associated with EC, which almost always is of well differentiated (grade1) type have ranged from about 5% to a little more than 25% of cases<sup>[8,13]</sup>. This wide variation was thought to be partly due to differing views on the dividing line between complex atypical hyperplasia and well differentiated (grade 1) adenocarcinoma<sup>[14]</sup>. In their study of 80 adult GCTs, Ali et al found 45% endometrial hyperplasia without atypia and 1.2% (a case) of endometrial adenocarcinoma<sup>[15]</sup>. Another study showed atypical hyperplasia in 1.6% and adenocarcinoma in 3.1% of cases<sup>[4]</sup>. Thus, if strict criteria for diagnosis of adenocarcinoma are used such that all the patients with GCTs are considered instead of just those that had undergone endometrial curettage or hysterectomy, the most probable incidence of an associated EC is below 5%<sup>[13,14]</sup>. Adult GCT peaks between 50 and 55 years with a median age at onset of 53 years, thus is known to occur more in postmenopausal than pre-menopausal women.

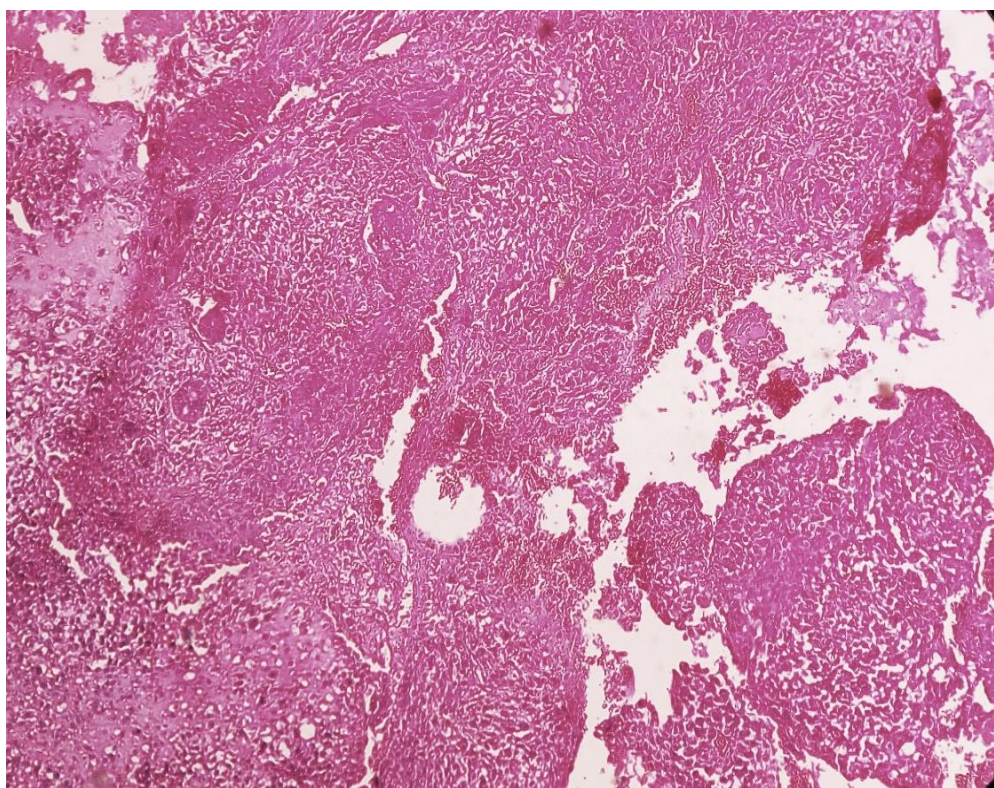
### II. Case Report

A 59year old Para2<sup>+</sup>2(2alive) Public servant and Christian of Ibo tribe who resides in Yenagoa, Bayelsa state, Nigeria presented at 4-year postmenopausal to Federal Medical Centre (FMC) Yenagoa on 18/08/17 with complaints of vaginal bleeding of 3months duration, lower abdominal pain and abdominal swelling of 18days duration. Vaginal bleeding was bright red to altered, mild to moderate but continuous with no passage of vesicles or bleeding from other orifices. Abdominal pain was generalized and affected her routine activities while abdominal swelling which started at same time was initially suprapubic but became generalized and radiated to the back. She was unaware of Pap smear for cervical cancer screening, never used oestrogen before neither had she been treated for infertility, pelvic inflammatory disease nor was there any past or present family history of gynecological cancer.

Her last child birth was 22years ago and she did exclusive breast feeding for her children. She never had surgery before or previous history of urinary symptoms, vaginal discharge, watery stooling, bone pains, headache or jaundice but she complained of chest pain with cough and evidenced weight loss with loss of appetite, easy fatigability, early satiety and dyspnoea on effort.

At onset of symptoms, she was managed at a private hospital in Aba, Abia State but due to worsening of her condition, she was taken to a private specialist clinic in Yenagoa where she had abdominopelvic scan, ascitic fluid cytology test and endometrial curetting for histopathologybased on ultrasound findings of a normal sized anteverted non-gravid uterus, 13.3 x 7.1 x 9.3cm with thick, mixed-echogenic endometrial content and a midline demonstrable echo.The left ovary also was enlarged with multiple cysts of which the largest measured 3.4 x 3.5cm. There was an associated ultrasonographic finding of massive ascitis. Cytopathologic diagnosis of the ascitic fluid aspirate was ovarian neoplasm of the granulosa cell type. Her ECG was essentially normal so in the light of the above findings, she was referred to FMC Yenagoa for expert care.Physical examination at presentation to FMCYenagoa revealed an average sized woman with normal vital signs and a blood pressure of 130/80mmHg, however she had a uniformly distended abdomen with presence of bowel sounds and organs were not palpable. Her cervix was central, hard and nodular with no contact bleeding. She was admitted as a case of ?Ovarian cancer, R/O Endometrial cancer on the 18/08/17 after review by Consultants. On the 21/08/17, a combined team of surgeons and gynecologists took her to theatre and she had staging laparotomy with bilateral salpingoophorectomy and omentectomy for stage IV ovarian cancer with noted findings of distant metastatic seedlings. Postoperatively she was managed by both the surgical and gynecological teams. She did well initially but later developed symptoms of post-operative intestinal obstruction with cough, paedal pitting oedema and elevated urea by the 10<sup>th</sup> day post-operative.

Her endometrial sample received for histopathology consisted of bits and pieces of brown, friable and haemorrhagic tissues aggregating 8.0 x 5.0 x 2.0cm with brown and haemorrhagic cut surfaces. Microscopic sections of these tissues showed areas of haemorrhage and necrosis within which are sheets of tumour cells of different sizes with some endometrial glands which are lined by malignant epithelial cells with marked nuclear atypia, loss of polarity and increased mitotic figures (Figure1).



**Figure 1:** Moderately differentiated (grade 2) endometrioid adenocarcinoma with some glands admixed with solid areas(H & E X100).

Diagnosis of moderately differentiated (grade 2) endometrioid adenocarcinoma was made. The left ovary received for histopathology was enlarged, measured 12.0 x 7.0 x 4.0cm and its cut surfaces showed yellowish bulbous growths into few large cystic spaces with rough and haemorrhagic mucosa (Figure 2).

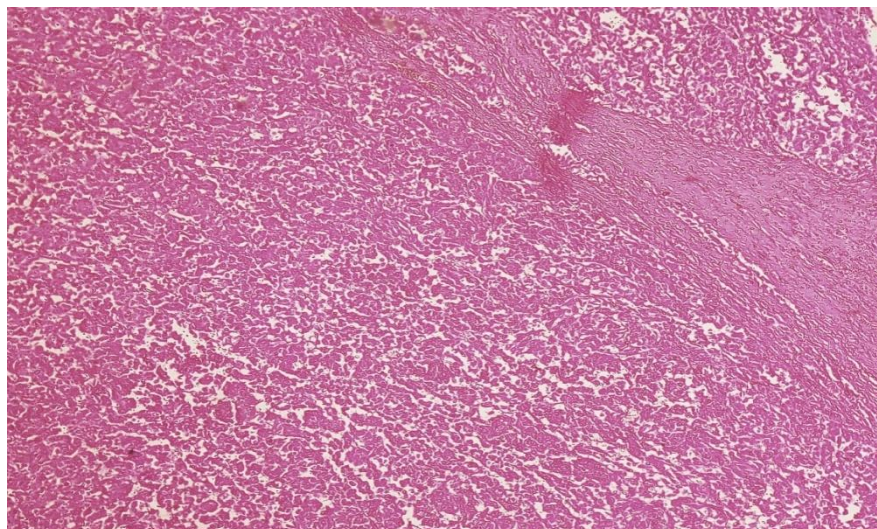


**Figure 2:** Cut surface of left ovarian mass showing solid ingrowths and few cystic spaces.



**Figure 3:** Omental tissue riddled with tumour seedlings.

Microscopically there were sheets of proliferating granulosa cells separated in places by fibrous ovarian stroma and invading the ovarian capsule. The sheets of tumour cells were punctuated by numerous Call-Exner bodies and many of the tumour cells nuclei were abutting on one another with characteristic nuclear groovings (Figures 4). A diagnosis of Adult GCT was also confirmed. The omentum (Figure 3) was diffusely infiltrated by sheets of granulosa cells exhibiting nuclear groovings and having structures with rosette-like arrangement of nuclei (Call-Exner bodies).



**Figure 4:** Section from left ovary showing granulosa cell tumour with tumour cells arranged in sheets punctuated by small follicle-like structures (Call-Exner bodies). (H & E X100)

The right ovary also showed a focus of contiguous spread of the tumour. Her serum CA-125 (cancer antigen-125) assay was 144.45units/ml against a reference range of 0 – 35units/ml. Inhibin assay was ordered early but was not done due to financial constraints. Despite all the efforts made by the managing teams, her clinical

condition continued to deteriorate with worsened ascites, pleural effusion and anaemia. She became severely dyspnoeic and gave up finally on the 24<sup>th</sup> day post-operative.

### III. Discussion

Though GCTs are uncommon, constituting only about 2 – 5% of ovarian cancers, they represent the most common estrogen-secreting ovarian tumours and are followed by thecomas, another sex cord-stromal tumour of the ovary<sup>[1,2,3,17,18]</sup>. Adult GCTs constitute about 95% of all the granulosa cell tumours<sup>[8,9,10,11,13]</sup>. We have seen only 4 isolated cases of GCT in our centre over nine years and all were of adult type. Two-thirds of GCTs occur in postmenopausal and pre-menopausal women and Adult GCT occurs more in postmenopausal than pre-menopausal women. The index case presented 4 years postmenopausal with vaginal bleeding. Abnormal vaginal bleeding is the most common presenting complaint in adults with GCT<sup>[4,5]</sup>. In cases of Adult GCT associated with endometrial pathologies like ours, the abnormal vaginal bleeding could be due to either GCT or both GCT and EC since they are all result from estrogenic effect. The index case was the first documented case of GCT associated with EC in our centre. With these 4 histopathologically documented cases of adult GCT, this puts the incidence of EC associated with adult GCT at 0.36% per year in our centre. This is in conformity with the actual range of less than 5% if strict criteria were used<sup>[13,14]</sup>. Type 1 carcinomas (comprising about 80% of cases) are associated with obesity, H

Hypertension, nulliparity with a history of infertility, late menopause, diabetes mellitus, tamoxifen therapy, estrogen-only therapy and use of sequential oral contraceptive pills<sup>[11,14]</sup>. Our case was an average sized, normotensive Para2<sup>+</sup> postmenopausal woman with no family history of diabetes mellitus or history of being treated for infertility. This most probably puts the histopathologically confirmed GCT as the only source of prolonged estrogen exposure in our case. GCTs are noted to cause EC because of continuous or prolonged and unopposed secretion of estrogen by the ovary<sup>[1,4,11,19]</sup>. The association of Adult GCT with grade 2 endometrioid adenocarcinoma in our case appears unique compared to most reported cases<sup>[8,13,14]</sup>. This however is not impossible even though it is said to be almost always grade 1. Also both grades 1 and 2 endometrioid adenocarcinoma are type 1 carcinomas and share same risk factors and associations<sup>[11,14]</sup>. The index case had an extensive GCT with wide omental and peritoneal seedlings thus the extent of the associated EC may equally be higher than grade 1 as seen. Our case had a markedly elevated level of serum cancer antigen-125 (CA-125). This tumour marker is known to be raised in 25% - 48% of cases of endometrial cancer. Normally serum levels of CA-125 tend to decline with age and onset of menopause with the concentration being lower in postmenopausal Asian and African women than their White counterparts<sup>[20]</sup>. The index case was a 4-year postmenopausal woman of African descent who had a highly elevated CA-125 level instead. This is quite significant and supports EC as the source. Inhibin assay remains a very relevant tumour marker for adult GCT but was not gotten due to financial constraints. However, CA-125 is the only tumour marker recommended for clinical use in diagnosis and management of ovarian cancer<sup>[21]</sup>.

### IV. Conclusion

Concomitant endometrial adenocarcinoma and adult ovarian granulosa cell tumour is rare. There is very scanty report of this association in our environment. This first case in our centre is reported to stimulate the Gynecologists in particular and Pathologists to have a high index of suspicion for the hyperestrogenic effects, most especially EC at or while making diagnosis of GCT. Diligent checking of the endometrial pathology in such cases should be the rule.

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