Junior researchers

ახალგაზრდა მკვლევარები

Vol. 2 No. 1, 2024

https://doi.org/10.52340/jr.2024.02.01.04

# კლინიკური შემთხვევა: საკვერცხის ბილატერალური ნათელუჯრედოვანი კარცინომა

*ნინო კიკვაძე[1]; ნინო კოჩუაშვილი[1]; თამარ ხმალაძე[1]; გიგი გორგაძე[1]; გიორგი დიდავა[2]; მარიამ გაბლიშვილი[3]*

1 - თბილისის სახელმწიფო სამედიცინო უნივერსიტეტის მედიცინის ფაკულტეტი, საქართველო;

2 - თბილისის სახელმწიფო სამედიცინო უნივერსიტეტის პათოლოგიური ანატომიის დეპარტამენტი, საქართველო;

3 - კლინიკური ონკოლოგიის ინსტიტუტი, თბილისი, საქართველო.

## აბსტრაქტი

66 წლის პოსტმენოპაუზურ პერიოდში მყოფმა ქალმა ექიმს მიმართა შემდეგი ჩივილებით: მუდმივი ყრუ ხასიათის ტკივილი მენჯის ღრუში, მუცლის გარშემოწერილობის გადიდება და მუდმივი სიმძიმის შეგრძნება, პერიოდული დიზურია. ანამნეზის მიხედვით დგინდება, რომ პაციენტს წარსულში დაუდგინდა ენდომეტრიოზი. ტრანსვაგინალური ულტრასონოგრაფიის, მცირე მენჯის ღრუს CT-სა და OC ონკომარკერის, CA125, შემოწმების შედეგების მიხედვით, პაციენტს დაუდგინდა უცნობი წარმოშობის საკვერცხის კიბოს კლინიკური დიაგნოზი.

პაციენტს ჩაუტარდა მიმოხილვითი ლაპაროტომია, ტოტალური აბდომინალური ჰისტერექტომია დანამატებთან ერთად და ომენტექტომია. პაციენტი კლინიკიდან გაეწერა პოსტოპერაციული პერიოდის მე-4 დღეს და დაენიშნა ქიმიოთერაპიული მკურნალობის შერჩეული 6 კურსიანი რეჟიმი.

ოპერაციული მასალის მაკროსკოპული კვლევისას იდენტიფიცირდა მარჯვენამხრივი სიმსივნური წარმონაქმნი უსწორმასწორო და კვანძოვანი ზედაპირით. ასევე, ორივე ფალოპის მილი აღმოჩნდა დილატირებული, განივკვეთზე მოყვითალო, ნეკროზული უბნებით. საშვილოსნოს განაკვეთმა აჩვენა შევიწროვებული ენდომეტრიუმის ღრუ მოთეთრო-მოყვითალო ინტრამურულ კვანძთან ერთად.

ოპერაციული მასალისაგან მომზადებული ნიმუშების მიკროსკოპულმა ანალიზმა და იმუნოჰისტოქიმიურმა კვლევამ დაადასტურა დიაგნოზი: საკვერცხის ბილატერალური ნათელუჯრედოვანი კარცინომა; ICD CODE_8310/3; PT2bNxMx (FIGO IB), ადენომიოზი (შიდა ენდომეტრიოზი), ინტრამურული ლეიომიომა.

საკვერცხის ნათელუჯრედოვანი კარცინომა საკვერცხის ეპითელური კიბოს იშვიათი ქვეტიპია და მოიცავს საკვერცხის კარცინომათა დაახლოებით 5-10%-ს. საკვერცხეების ავთვისებიანი ტრანსფორმაციის მოლეკულური მექანიზმების გასარკვევად და მისი კავშირის შესასწავლად ენდომეტრიოზის ან მენჯის ქრონიკული ანთების ისტორიასთან, აუცილებელია, ისეთი გენეტიკური აბერაციების როლის დადგენა OCCC-ის გენეზში, როგორიცაა მაგალითად ARID1A გენის ფუნქციის დაკარგვის მუტაცია. ისევე, როგორც, მნიშვნელოვანია სპეციფიკური იმუნოჰისტოქიმიური მარკერების განსაზღვრა, რომლებითაც შესაძლებელი იქნება CCC-ის ადრეული დიფერენცირება სხვა ტიპის OC-ებისგან კლინიკურ პრაქტიკაში. გარდა ამისა, OCCC-ის განვითარების მოლეკულური გზების უფრო ღრმა ცოდნა, მოგვცემს შესაძლებლობას, შემუშავდეს მკურნალობის ალტერნატიული სტრატეგიები პაციენტების გადარჩენის შანსების გაზრდის მიზნით და დაინერგოს დაავადების სკრინინგ-პროგრამა მისი ადრეული დიაგნოსტიკისთვის, რადგან, სამწუხაროდ, ეს უკანასკნელი, მიუხედავად მრავალი მცდელობისა, კერ კიდევ მნიშვნელოვან გამოწვევად რჩება ონკოლოგიაში.

**საკვანძო სიტყვები:** საკვერცხის ნათელუჯრედოვანი კარცინომა, ენდომეტრიოზი, ადენომიოზი.

## A Case Report: Bilateral Ovarian Clear-cell Carcinoma

*NINO KIKVADZE [1]; NINO KOCHUASHVILI [1]; TAMAR KHMALADZE [1];GIGI GORGADZE [1]; GIORGI DIDAVA [2]; MARIAM GABLISHVILI [3]*

1 - Faculty of Medicine of Tbilisi State Medical University, Georgia;
2 - Anatomical Pathology Department of Tbilisi State Medical University, Georgia;
3 - Institute of Clinical Oncology Tbilisi, Georgia;

### Abstract

A 66 years old female presented with persistent deaf pain in small pelvis, enlarging abdominal and periodic dysuria. She had a past gynecological history of endometriosis. According to the results of transvaginal ultrasonography, small pelvis CT and the check-test answers of OC oncomarker CA125, clinical diagnosis of unknown origin ovarian cancer was offered. The patient underwent an exploratory laparothomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy.

An intra-operative frozen section of the pelvic mass was positive for OC. During the post-operative examination of ovaries and uterus, in addition of solid ovarian tumor a cut surface of uterus showed a whorled intramural nodule. Microscopic features on cytology examination of ascetic fluid was negative for malignant cells. Microscopically, both ovaries showed typical features of CCC. Apart

from this, according to the additional IHC analysis the diagnosis of bilateral ovarian clear cell carcinoma was confirmed.

Ovarian clear cell carcinoma is a rare subtype of epithelial ovarian cancer and comprises about 5-10% of ovarian carcinomas. To elucidate of molecular mechanisms underlying the malignant transformation of ovaries and investigate its relationship with past-history of endometriosis or chronic pelvic inflammation, it is essentialto observe the genetic pathways such a ARID1A-loss mutation role in genesis of OCCC, as well as, specific immunohystochemical markers by which OCCC is characterized to differentiate CCC from other types of OCs for an early diagnosis in clinical practice. Furthermore, greater understanding of molecular pathways of OCCC provide opportunities to develop alternative treatment strategies with the aim of improving survival chances of patients with OCCC, also for an early diagnosis of OCs to introduce and implement a screening program, which despite many attempts, remains a significant challenge in oncology.

**Keywords:** ovarian clear cell carcinoma, endometriosis, adenomyosis.

## Introduction

Ovarian cancer (OC) is the eighth leading cause of cancer mortality among women and the seventh most common cause of cancer diagnosis worldwide. In spite of the improvement of novel treatments for OC patients, that has been made in recent years, 70 % of patients with OC are diagnosed at a middle or advance stage, which leads a high mortality rate of OC. The main reasons of late diagnosis are the lack of specific clinical signs or symptoms and effective or sensitive clinical detection methods in the early stage. The five-year survival rate of OC patients is below 45% [1].This is mainly because this cancer gets diagnosed at stage III or IV with metastasis and it also has a high recurrence rate after standard therapy in 70% of cases. Additionally, the lack of anatomical barrier around the ovaries facilitates the dissemination of OC cells into peritoneal cavity, metastasizing onto abdominal organs resulting in bowel obstruction, which is the major cause of OC morbidity and mortality [2].

In 2020, according to the data of the cancer registry of Georgian National Center for Disease control and Public health, in women 269 new cases of ovarian malignant neoplasms have been reported. Generally, ovarian neoplasms take 11$^{th}$ place in the list of malignant neoplasms in our country. It is also noteworthy, that from 2015 to 2020a relative decrease in the number of new cases of ovarian ovarian malignant neoplasms is observed (2015_343 new cases; 2020_269 new cases), but in recent years (2018-2020), this number has remained relatively stable, averaging around 270 new cases per year [9]. It should also be mentioned, that unlike screening programs for breast and cervical cancer, no screening program has been introduced for the early diagnosis of malignant ovarian neoplasms, that, of course, correlates with delayed diagnosis of cancer and poor prognosis. This problem remains a major challenge for the modern oncology [10].

Most OCs manifest post menopause and the increased incidence are reported in women older than 65 years. Considering the ethnicity, non-Hispanic white women are reported to have the highest

incidence and mortality rates [3]. OCs are heterogeneous cancer, hence the risk factors for each histological subtype vary. In general, some of the major risk factors for OC include Hereditary Breast and Ovarian Cancer (HBOC) syndrome, menopausal hormonal therapy, endometriosis, use of fertility drugs, late menopause and null parity. Other emerging risk factors are also the use of talc powders, asbestos exposure and pelvic inflammatory disease. Interestingly, high parity, hysterectomy and usage of hormonal contraceptive pills for prolonged periods, as well as, the sterilization treatment, tubal ligation, are reported to reduce the risk of OCs [4; 5].

OC neoplasms arise from distinct regions of ovary. They are termed heterogeneous as each OC subtype is unique with varied morphology, biologic behavior and even prognosis. OCs are broadly classified into epithelial and non-epithelial cancers(Fig 1). Non-epithelial cancer includes germ cell cancer, stromal cell cancer and the rare cell carcinoma. Epithelial ovarian cancers (EOCs) account for more than 9 in 10 of these cases and are among the most-characterized forms of OCs. More than half of EOC cases affect people over 65, thus it is considered mainly a postmenopausal disease. In cases of EOCs malignant cells arise from the epithelium covering the ovary or lining the fallopian tubes. Based on tumor cell morphology, they are further subdivided into high grade serous ovarian carcinoma (HGSOC), low grade serous ovarian carcinoma (LGSOC), mucinous ovarian carcinoma (MOC), endometrioid carcinoma (EC) and clear-cell carcinoma (CCC) [6]. Clear-cell carcinomas are a distinct class of EOCs thought to arise from endometriosis or clear cell adenofibroma, hence they are associated with endometriosis which is thought to be the precursor for CCC manifestation and this association is considered a good prognosis. The highest risk-factors for developing CCCs are late menopause and endometriosis. CCCs of the ovary constitute more than 5% of all OCs and 10% of all EOCs. The most dangerous age for developing CCCs is the age between 50-70 years. What about the prognosis, these are chemoresistant tumors with a poor prognosis if it is diagnosed at an advanced stage, but most of these cases are diagnosed early with a good prognosis. The most common chromosomal aberrations identified in CCCs are activating mutations in *PIK3CA*, a regulator of the *PI3K-PTEN-AKT* pathway (50%), and loss of the function in *ARID1A* component of *SWI/SNF* chromatin remodeling complex (50%) [7].

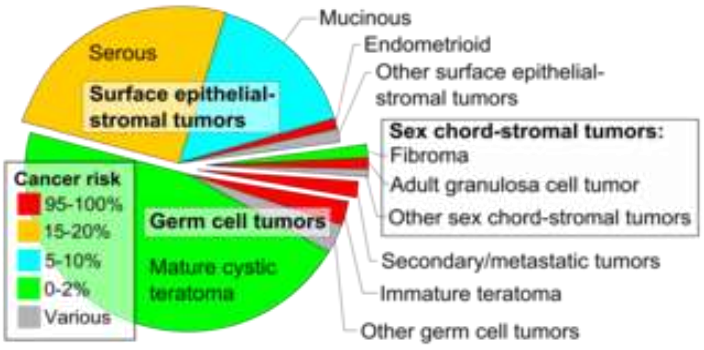



**Figure 1.** Origin of the various ovarian cancer subtypes and their percentage statistics. [11]

## Case Report

Here, we describe a case report of bilateral ovarian clear-cell carcinoma (CCC) in 66-year-old postmenopausal female with a past gynecological history of endometriosis.

A 66-year-old postmenopausal multiparous, female presented to gynecologic outpatient department with history of persistent deaf pain in small pelvis, abdominal distension, increase in size, periodic dysuria. From recent illness history, the patient complained of no appetite since 1 month before admission to the hospital, vomiting and a little urinating, the patient also enlarging alternating abdominal pain since 1.5 month before entering the hospital. Past gynecological history was remarkable for endometriosis. Past medical, surgical, family and social histories were non-contributory. The patient was consulted by a gynecologist at the clinic and had an objective examination. On physical exam, her abdomen was distended, diffusely tender, dull to percussion and positive for both rebound and guarding. Her pelvic exam was remarkable for cervical motion tenderness and diffuse tenderness. Bimanually, in the small pelvis, especially in the pelvis, a palpable, dense, voluminous formation was examined. It was impossible to examine the uterus and ovaries separately. The patient underwent transabdominal and transvaginal ultrasonography , small pelvis and abdominal CT, CT of thorax and aspiration biofsy of ascetic fluid with cytological examination.

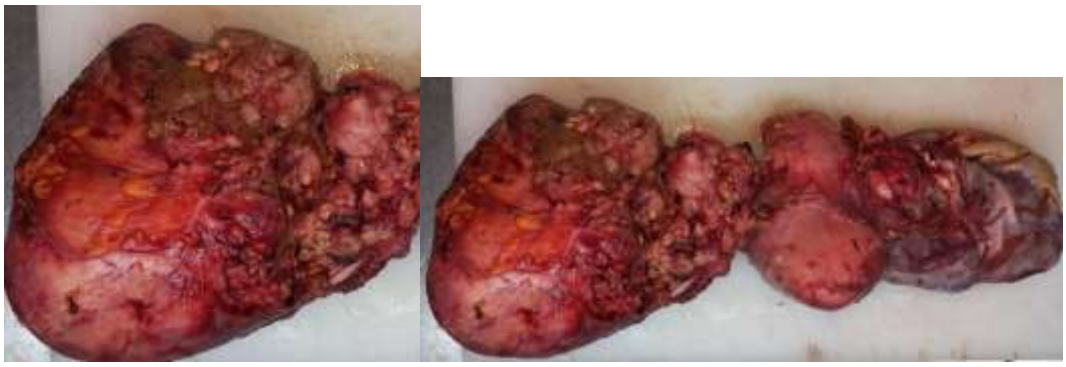
Her routine hematological and biochemical analysis were within normal limits. A radiological diagnosis of ovarian neoplasm was offered. An abdominal X-ray was negative for free air. An abdominal and thorax CT were in frames of normal limits. Small pelvis CT and transvaginal ultrasound showed heterogenous, mostly solid formations, bilaterally on the projection of both appendages. Asceticfluid sent for cytology was negative for malignant cells. The liver, spleen, pancreas and appendix appeared normal.

According to the results of transvaginal ultrasound examination, small pelvis CT and positive answers of check-test for oncomarker CA125 (385,17 U/ml (0-35 U/ml)) the clinical diagnosis of ovarian cancer of unknown origin was offered. Which then by the microscopic and immynohistochemical analysis has been differentiated as an ovarian clear-cell carcinoma. The patient ultimately underwent an exploratory laparotomy, total abdominal hysterectomy, bilateral salpingo-oophoretomy, excision of the pelvic mass and omentectomy. An intra-operative frozen section of the pelvic mass was performed and was positive for ovarian carcinoma. The patient's post-operative course was uncomplicated, she was discharged home on post-operative day 4. The patient's case was discussed at clinical multidisciplinary tumor board and the recommendation is for her to be threatened with a 6-course regimen of systemic aduvant chemotherapy with carboplatin and paclitaxel.

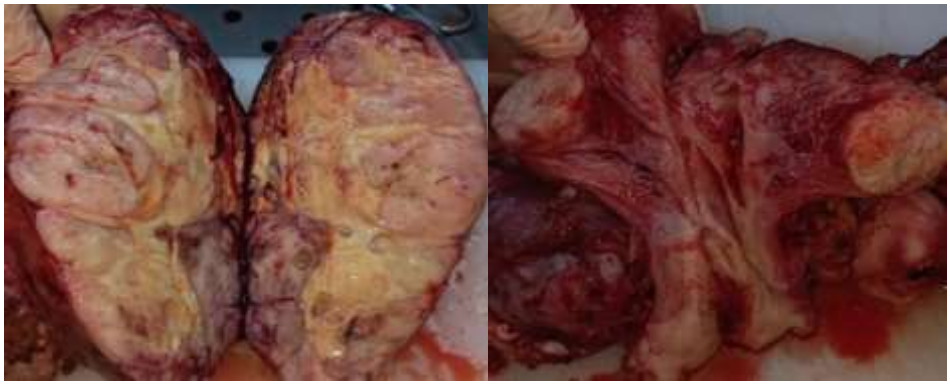
## Gross Examination

The right adnexal mass measured 105mm x 75mm x 45mm. external surface was nodular. Cut surface showed predominantly solid mass with yellowish and few whitish areas. Right and left fallopian tube were dilated, the cut section of which showed yellowish necrotic material. Cut surface of the uterus showed distorted endometrial cavity with whitish, firm and whorled intramural nodule measuring 49mm x 45mm x 50mm. Cervix measured 25mm in length and was unremarkable. The left ovary

measured 120mm x 80m x 70mm and the right ovary measured 170mm x 120mm x 100mm, the cut surface of which showed white-pink areas. Appendix, omentum and peritoneal biopsy specimen were received. They appeared grossly congested and otherwise unremarkable. Microscopic examination showed typical features of OCCC.



A;B



C;D

**Figure 2. A** Right ovary (size: 170x120x100mm) with right adnexal mass which measured 105x75x45mm.
**B** - right and left ovaries with right adnexal mass and uterus.
**C** - The cut surface of solid adnexal mass with yellowish and few whitish areas.
**D** - Whitish, firm and whorled intramural nodule (size: 49x45x50mm) is showed on the cut surface of the uterus.

**Methods:**

With the help of the pathanatomy laboratory of Anatomical Pathology Department of Tbilisi State Medical University, all samples were formulated with paraffin and implanted with paraffin, they were cut into 4 mm thick serial sections and analyzed by immunohistochemistry. Commercially available polyclonal rabbit anti-ARID1A antibody was used as the primary antibody for ARID1A protein detection. Deparaffinized sections were boiled in an autoclave at 120$^0$C for 18 min in a 0.01 mol/L citrate buffer and then cool to room temperature. Antigen-antibody reactions were visualized with 0.2% diaminobenzidine tetrahydrochloride and hydrogen peroxide and counterstaining was performed using hematoxylin. Cells, including endothelial cells, fibroblasts and lymphocytes, normally show ARID1A nuclear immunoreactivity and therefore, they served as positive internal controls. In addition, immunohistochemistry (IHC) was performed with the following panel of antibodies: WT1 (Wilm's tumor gene); EMA (epithelial membrane antigen); ER (estrogen receptor); PR (progesterone receptor); P53 and Napsin-A (a cytoplasmic aspartic protease, which is

predominantly expressed in lung and kidney; the specifity and sensitivity for Napsin-A by IHC for distinction of OCCC and ECCC from non-CCCs was 100% confirmed by recent stydies).

**Microscopic Examination**

Microscopically both ovaries showed typical features of CCC.In the tumor tissue of both ovaries fibrous stroma in which the alveolar-solid proliferations of large, hyperchromatic nuclei and atypical cells with clear-eosinophilic cytoplasm are infiltrated. There was also focus necrosis and bleeding. In the myometrium are noted place of adenomyosis (internal endometriosis). Intramural node shows smooth muscle cell proliferation without atypia. No atypical cells are observed in adipose tissue.

Immunohistochemistry for ARID1A Detection research have shown that inactivating mutations of ARID1A are associated with the loss of protein expression. We focused our attention on the lesions with undetectable ARID1A immunoreactivity in the nucleus and used a scoring system to classify all lesions into ARID1A deficient. Apart from this, by the IHC the both ovarian tumor tissue showed positivity for P53 , CK7, EMA and Napsin-A; no immunoreactivity for WTA1 and PR. That help us to differentiate CCC from other types of OCs, especially from HGSCs and thus, based on IHC studies and microscopic analysis the diagnosis of OCCC in both ovaries, with adenomyosis (internal endometriosis), intramural leiomyoma in uterus was confirmed.

Diagnosis: Bilateral ovarian clear-cell carcinoma; ICD CODE_8310/3; P T2bNxMx (FIGO IB); Adenomiosis (internal endometriosis); intramural leiomyoma.

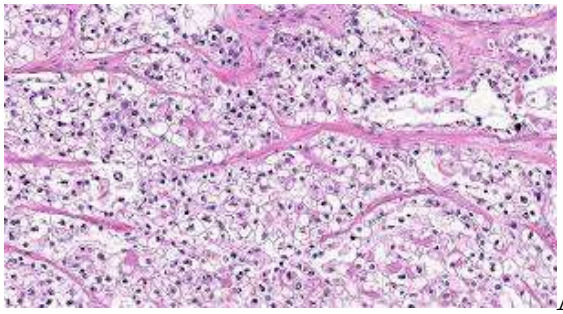
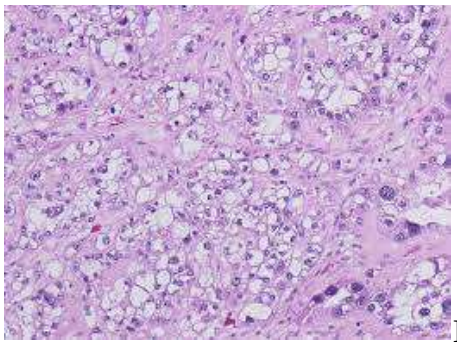
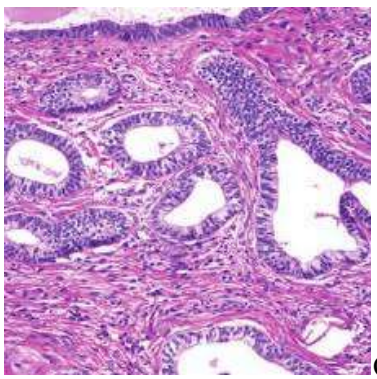
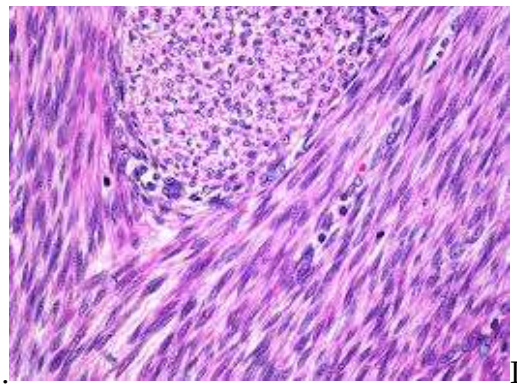

A.

B.

C.

D.

**Figure 3. A,B** - in the tumor tissue fibrous stroma with alveolar-solid proliferations of hyperchromic nuclei and atypical cells with clear cytoplasm.
**C** - atypical polipoid adenomyoma, biphasic with hyperplastic and atypical endometrial glands. **D** - intramural node(leiomyoma) shows smooth muscle cell proliferation witout atypia.

## Discussion

In the ovaries, endometrioid cancer represents the most known example of an epithelial malignancy arising from endometriosis, followed by clear cell carcinoma. On the other hand, serous and mucinous adenocarcinomas are prevalent in ovarian cancers unrelated to endometriosis.[12]

To elucidate the molecular mechanism underlying the malignant transformation of endometriosis, and considering the important role of genetics in the development of both endometriosis and ovarian cancer, many studies thus far have attempted to evaluate whether endometriosis-associated genetic alterations or gene polymorphisms increase the risk of ovarian cancer. Notably, strong evidences of a genetic link between endometriosis and ovarian cancer have been detected thus far. Loss of heterozygosity at 10q23.3 and mutations leading to functional inactivation of the PTEN gene as well as ARID1A, PIK3CA, CTNNB1 (β-catenin), TP53 and K-ras gene mutations have been shown to contribute to endometriosis-associated ovarian cancer [13]

To date, two significant mutational/expressional molecular characteristics of O-CCC have been found, ARID1A loss and HNF1β-overexpression.[14]

For ARID1A, its loss is suggested as a critical event in endometriosis (EM)-derived O-CCC tumorigenesis.[15]

Indeed, ARID1A loss has been noted in O-CCC associated atypical EM tissues, as well.Since ARID1A is a major component of the human SWI/SNF chromatin-remodeling complex,its oncogenic role may be related with remodeling of chromatin and histone re-arrangements or with modulation of estrogenic action. [16]

It was found that ARID1A-loss in O-CCC is linked to a specific immunohistochemical profile: ERβ loss, intact E-cadherin, and HNF1β overexpression. ERβ expressional loss occurs frequently across all epithelial ovarian cancers, and ARID1A is important in carrying steroid hormone signaling to the SWI/SNF-induced transcriptional activations.[17]

We suspect a hidden significance of HNF1β overexpression here. The functional role of HNF1β overexpression in O-CCC has not yet been derived,although it may also be mediated by E-cadherin: knock down of HNF1 has been shown to reduce E-cadherin expression and promote epithelial-mesenchymal transition.[18]

Thereafter, we argue that this signaling axis, ERβ/ARID1A/E-cadherin along with HNF1β, requires further molecular functional studies to elucidate the mechanism of O-CCC development.

In addition, we were able to understand that in the majority of ARID1A-deficient carcinoma cases, ARID1A immunodeficiency was already evident in the absence of cytological atypical precursor stage, suggesting that ARID1A protein loss occurs as a very early event in tumor genesis.

Loss of ARID1A expression and PIK3CA mutations frequently coexisted and were not mutually

exclusive. Although in the current study the mutational status of the ARID1A gene was not known, in ovarian clear-cell carcinomas, the presence of ARID1A mutations were adequately, but not perfectly, correlated with the loss of ARIDA1 immunoreactivity.[19]

Notably, several observations, mainly epidemiologic, suggest that females who have been exposed to chronic pelvic inflammation seem to be at an elevated risk for the development of epithelial ovarian cancer.[20]

This observation suggests that the pathogenesis of endometrioid cancer is marked from that of other epithelial malignancies of the ovary. Moreover, it is hypothesized that a correlation may exist between ovarian endometriomas and malignant endometrioid tumors.

In conclusion, our case and these findings indicate once again that women with endometriosis have an increased risk for several types of ovarian cancers, more frequently endometrioid carcinoma and according our case for OCCC. Furthermore, additional studies are essential to observe ARID1A-loss role in genesis of OCCC, as well as, specific immunohystochemical markersby which OCCC is characterized to differentiate this type of ovarian cancer from other types of epithelial carcinomas, for the early diagnosis of patients in clinical practice. In addition,further research is required to establish the relationship between endometriosis, especially, based on the case described above, the internal endometriosis (adenomyosis), and the ovarian malignancies.

## Future directions:

The improved definition of ovarian clear cell carcinoma, and greater understanding of its molecular characteristics, provide opportunities to develop alternative treatment strategies with the aim of improving survival, particularly of patients with advanced-stage or recurrent disease. Due to the rarity of clear cell carcinoma, international collaboration will be essential to power large-scale clinical trials required to answer the many remaining questions regarding the optimal treatment of this disease. Accurate diagnosis, particularly the exclusion of clear cell carcinoma mimics such as high-grade serous carcinoma with clear cells, will be crucial for these trials to produce reliable findings. Specific areas that merit further investigation include the relationship between mismatch repair (MMR) deficiency and response to immune checkpoint inhibitors, the prevalence of BRCA mutation and its relationship to poly-ADP ribose polymerase (PARP) inhibitor response, and the development of novel therapies based on tumor biology.

In addition, it should be noted once again that there is an obvious need for ovarian tumor screening, which, despite many attempts, remains a significant challenge in oncology.

## References:


1. Yaogang Wang & Zhigao Chen (2022) Long noncoding RNA UBA6-AS1 inhibits the malignancy of ovarian cancer cells via suppressing the decay of UBA6 mRNA, Bioengineered, 13:1, 178-189
2. Ravindran, F., & Choudhary, B. (2021). Ovarian Cancer: Molecular Classification and Targeted

Therapy. In G. Ho, & K. Webber (Eds.), Ovarian Cancer - Updates in Tumour Biology and Therapeutics. IntechOpen.
3. Torre LA, Trabert B, DeSantis CE and others. Ovarian Cancer Statistics, 2018. CA Cancer J Clin 2018; 68: 284-296
4. Lundberg FE, Iliadou AN, Rodriguez-Wallberg K, et al. The risk of breast and gynecological cancer in women with a diagnosis of infertility: A nationwide population-based study. Eur J Epidemiol 2019; 34: 499-507
5. Michels KA, Brinton LA, Pfeiffer RM, et al. Oral Contraceptive Use and Risks of Cancer in the NIH-AARP Diet and Health Study. Am J Epidemiol 2018; 187: 1630-1641
6. Desai A, Xu J, Aysola K, Qin Y, Okoli C, Hariprasad R, Chinemerem U, Gates C, Reddy A, Danner O, Franklin G, Ngozi A, Cantuaria G, Singh K, Grizzle W, Landen C, Partridge EE, Rice VM, Reddy ES, Rao VN. Epithelial ovarian cancer: An overview. World J Transl Med. 2014 Apr 12;3(1):1-8. PMID: 25525571; PMCID: PMC4267287.
7. Robbins "Basic Pathology" , 10th Edition;
8. Khandeparkar, S. G., Deshmukh, S. D., Lekawale, H. S., Bhoge, A., & Ahmed, A. T. (2014). A rare case of synchronous right ovarian clear cell carcinoma and an incidental left ovarian endometrioid carcinoma with immunohistochemical study. *Journal of mid-life health*, *5*(2), 91–94.
9. NCDC-HEALTH CARE STATISTICAL YEARBOOK.2020 (Fig. 5.29; pg67_canser new cases by sites, Georgia);
10. Center of Cancer Research UK. The Article "Screening for Ovarian Cancer", last reviewed_22Dec.2021;
11. Ovarian tumors by incidence and cancer risk.svg. (2020, October 30). *Wikimedia Commons, the free media repository*. Retrieved 11:51, April 9, 2022
12. Vercellini P, Scarfone G, Bolis G, Stellato G, Carinelli S and Crosignani PG: Site of origin of epithelial ovarian cancer: The endometriosis connection. BJOG. 107:1155–1157. 2000.
13. Sato N, Tsunoda H, Nishida M, Morishita Y, Takimoto Y, Kubo T and Noguchi M: Loss of heterozygosity on 10q23.3 and mutation of the tumor suppressor gene PTEN in benign endometrial cyst of the ovary: Possible sequence progression from benign endometrial cyst to endometrioid carcinoma and clear cell carcinoma of the ovary. Cancer Res. 60:7052–7056. 2000.
14. Jones S, Wang TL, Shih IeM, Mao TL, Nakayama K, Roden R, et al. Frequent mutations of chromatin remodeling gene ARID1A in ovarian clear cell carcinoma. Science. 2010;330:228–231.
15. Xiao W, Awadallah A, Xin W. Loss of ARID1A/BAF250a expression in ovarian endometriosis and clear cell carcinoma. Int J Clin Exp Pathol. 2012;5:642–650.
16. Wiegand KC, Shah SP, Al-Agha OM, Zhao Y, Tse K, Zeng T, et al. ARID1A mutations in endometriosis-associated ovarian carcinomas. N Engl J Med. 2010;363:1532–1543.
17. Lin K, Zhan H, Ma J, Xu K, Wu R, Zhou C, et al. Increased steroid receptor RNA activator protein (SRAP) accompanied by decreased estrogen receptor-beta (ER-β) levels during the malignant transformation of endometriosis associated ovarian clear cell carcinoma. Acta

Histochem. 2014;116:878–882.
18. Tomassetti A, De Santis G, Castellano G, Miotti S, Mazzi M, Tomasoni D, et al. Variant HNF1 modulates epithelial plasticity of normal and transformed ovary cells. Neoplasia. 2008;10:1481–1492.
19. Maeda D, Mao TL, Fukayama M, et al. Clinicopathological significance of loss of ARID1A immunoreactivity in ovarian clear cell carcinoma. Int J Mol Sci 2010;11:5120–5128.
20. Ness RB: Endometriosis and ovarian cancer: Thoughts on shared pathophysiology. Am J Obstet Gynecol. 189:280–294. 2003.