International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Paulose MK et al. Int J Reprod Contracept Obstet Gynecol. 2024 Oct;13(10):2940-2946
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20242838

Case Report

Endometrioid carcinoma arising from the remnant ovarian tissue

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Received: 24 July 2024
Revised: 18 August 2024
Accepted: 21 August 2024

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ABSTRACT

Endometrioid carcinoma of ovary is a subtype of epithelial tumours of the ovary. It can be distinguished from serous and mucinous tumours by presence of tubular glands resembling that of malignant endometrium. Traditionally, Ovarian carcinoma treatment involves the combination of cytoreductive surgery and platinum-based chemotherapy. Fortunately, because of a better overall understanding of ovarian tumorigenesis and advancements in the disease's epigenetic and molecular profiling, a paradigm shift has emerged with the identification of new disease biomarkers and the proposal of targeted therapeutic approaches to postpone disease recurrence and decrease side effects, while increasing patients' survival. It is usually associated with poor prognosis due to late clinical presentation allied with the common acquisition of chemo resistance and a high rate of tumour recurrence. The chemotherapy backbone for patients with high-grade advanced epithelial ovarian cancer (HG-AOC) is carboplatin and paclitaxel followed by a maintenance therapy either with bevacizumab, with a PARP inhibitor, or with a combination of both, which is defined by the presence of a Homologous Recombination Deficiency (HRD) and by the BRCA1/2 status (This case showed a negative HRD and BRCA1/BRCA2 mutation status). Hence effective screening, accurate diagnosis and personalised multidisciplinary treatments are crucial for improving patient's survival and quality of life. We report a case of endometrioid carcinoma of ovary arising from the remnant ovarian tissue in a 53year old women who underwent TAH+BSO done 12 years back for a benign cause and aims to summarize molecular studies involved in endometroid ovarian carcinoma pathogenesis as potential therapeutic targets.

Keywords: Chemotherapy, Endometrioid carcinoma, Molecular studies

INTRODUCTION

Endometrioid ovarian tumours are classified under epithelial tumours of ovary and it accounts for about 10% of all primary ovarian cancers. It is a neoplasm closely resembling endometrial endometrioid adenocarcinomas.[1] Endometrioid tumours are sub classified as benign, borderline and malignant neoplasms. Women with endometrioid ovarian cancer presents at the younger age and with earlier stage disease when compared with other ovarian cancers. Coexistent endometriosis can often be demonstrated and some of the tumours can be seen arising from those endometriotic foci.[2]

CASE REPORT

A 53-year-old female presented with complaints of right sided abdominal pain, abdominal discomfort and urinary

incontinence of two-week duration. She has 2 previous full term normal vaginal delivery, Last child birth 25 years back, no comorbidities. She underwent TAH+BSO+appendicectomy in 2012 for fibroid uterus with severe endometriosis. No other family member has ovarian, gastro intestinal or any other malignancies for the past two generations.

Intra-operative findings of TAH+BSO

Uterus 10-12week size with large anterior fibroid and Dense adhesions were present. Pouch of Douglas obliterated with adhesion between sigmoid colon and caecum to both ovaries and uterus. Right ovary densely adherent to the caecum. Black powder burnt endometriotic deposits seen over bladder peritoneum. TAH+BSO+adhesiolysis+appendicectomy done. Small bits of right ovarian tissue left with caecum which could not be removed.

Patient did not follow up further and later presented In 2014 with abdominal discomfort and on evaluation USG showed a multi septate complex cystic lesion measuring 8.8cm×7.8×8.1 cm in the right side of pelvic cavity closely abutting and displacing surrounding small bowel loops and caecum- endometriotic cyst or cystic ovarian neoplasm from residual ovarian tissue with normal CA-125, CEA and CA-19.9 reports. Patient was not willing for surgical intervention at this point of time and lost to follow up for another two years.

Again, presented in 2016 with similar complaints and increase in abdominal pain imaging showed increase in size of the lesion. She was managed with injection depo Provera 150mg IM 3 doses at 3 monthly intervals. Patient was kept under follow up as she was not willing for surgery. In November 2023 she was again admitted with complaints of abdominal pain, abdominal distension and urinary retention.

On examination vitals were stable with no other systemic findings. On abdominal examination- immobile globular cystic firm hard mass of size palpable extending from right hypochondrium to right iliac fossa. Per speculum examination revealed vault pulled up, per vaginal examination showed cystic fullness in right adnexa with immobile fornices.

Investigations

Base line investigations were normal with elevated tumor markers. CA-125-125.2 U/ml, CA-19.9-549 U/ml, CEA-6.05 ng/ml.

USG (abdomen and pelvis)

Uterus-post hysterectomy status, ovaries not visualized. Multi loculated cysticlesion in the right pelvic wall (8×7.5×5.4 cm) with septations, soft tissue components and mild internal vascularity noted. Mild right hydronephrosis likely due to extrinsic compression over right ureter.

Urology opinion was sought regarding ureteric compression and advised CECT urogram, which showed Large well defined pelvic cystic lesion (11×10.4×10.7 cm) towards the right adnexa with multiple internal septations and intervening irregular shaped hyperdense areas showing post contrast enhancement.The cystic lesion shows peripheral vascularity along its lateral and posterior aspects with blood vessels seen directly arising from the infra renal abdominal aorta, internal iliac artery and vein-features likely suggestive of right malignant ovarian neoplasm. Sub centimetric bilateral external iliac, mesenteric, paraaortic and aortocaval lymph nodes. Right mild hydroureteronephrosis-likely due to compression or adhesions of distal ureter with aforementioned adnexal lesion.

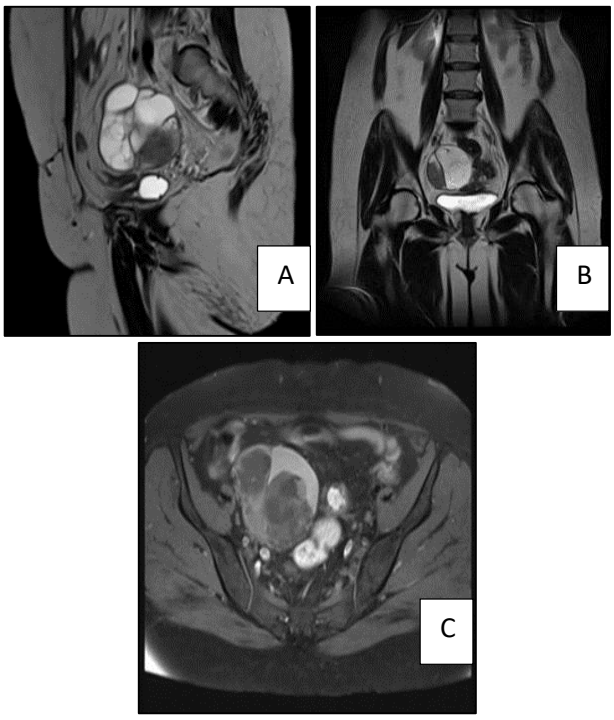

Figure 1 (A-C): Right adnexal multiloculated cystic lesion.

MRI pelvis

Right adnexal multiloculated cystic lesion measuring 12×8×7 cm. lesions show multiple loculations with varying signal intensities. Well defined enhancing soft tissue component along the inferolateral aspect of the cystic lesion-likely representing the residual right ovarian tissue. Right distal ureter seen draped close to the posterolateral aspect of the cystic lesion and could not be separately delineated from the cyst-possible adhesions. mildly prominent partially extra renal bilateral renal pelvis. Terminal ileum seen closely abutting the Antero inferior and inferior aspect of the right adnexal cystic lesion-suspicious of adhesions. O-RADS score-5.

Procedure

Underwent emergency exploratory staging Laparotomy with right complex adnexal cyst excision (frozen section suggestive of malignant ovarian neoplasm) followed by omentectomy+right and left external iliac, internal iliac, obturator and right paraaortic lymph node dissection+terminal ileal resection.

Intra-operative finding

A large cystic lesion of size 14x9x8 cm arising from right ovarian fossa, adherent to right lateral pelvic wall and posteriorly to ileum. ureter seen in proximity with the cyst.

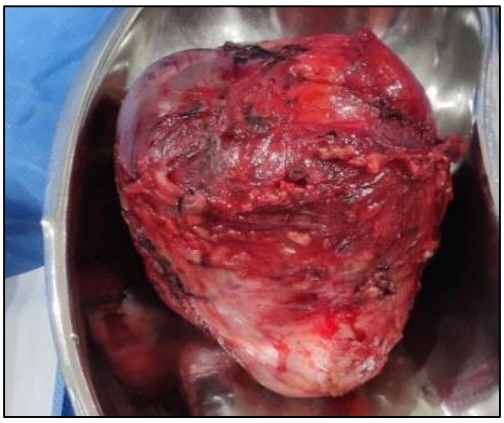

Figure 2: Intra operative finding-large right adnexal cystic lesion.

Histopathological report

Globular cystic lesion measuring 13.5×7×8 cm with smooth surface and intact capsule. Cut section showed multi loculated cyst with focal solid areas with granular grey white to brown appearance. Cut section of adherent portion of intestine shows oedematous mucosa with areas of congestion.

Microscopy

Infiltrating neoplasm composed of tumor cells in complex glandular papillary, micro papillary, cribriform and solid patterns surrounded by desmoplasia. Mitotic activity- 6 to 8 per 10 HPFs Suggestive of endometrioid carcinoma ovary-grade2 (moderately differentiated) 13.5×7×8 cm size with no extra capsular extension, lymph vascular invasion or peri neural invasion. 3 out of 17 regional lymph node (two right obturator lymph nodes and one right para-aortic lymph node) showed metastatic deposit. Endometriosis seen in the rest of adjacent ovarian stroma. Neoplasm is adherent to the serosal aspect of the intestine but not invading in to it.

Final diagnosis

Endometroid carcinoma ovary-FIGO stage 3C. BRCA1 and BRCA2 mutation negative. TNM staging-pTINI.

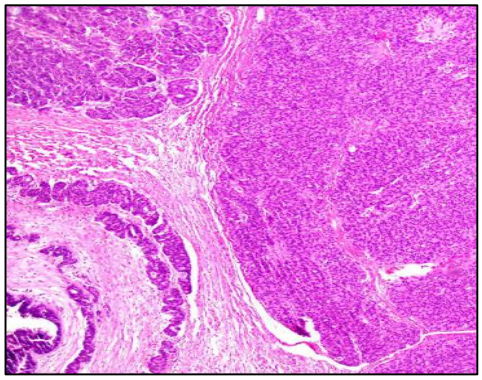

Figure 3: Neoplastic glands with solid areas.

Adjuvant treatment

Case was discussed in gynaecology Multidisciplinary tumor board and plan was taken for adjuvant platinum-based chemotherapy. Patient received 6 cycles of Paclitaxel (175mg/m^2) and carboplatin (AUC-5) 3 weekly-completed in march 2024. She was also planned for BRCA somatic germ line testing along with HRD testing. She was kept under regular follow up. First follow up done after one month of completion of chemotherapy with Ca 125 value of 11.8 U/ml.

DISCUSSION

Endometrioid carcinoma of ovary affects 5th and 6th decade of life. About 42% of tumours associated with endometriosis of same ovary and 15-20% co-exist with endometrial carcinoma.[3] When it is associated it affects 10 years younger women on an average.[4] Hyper estrogenic states have a role in the transformation of endometriosis.[5] Many are asymptomatic and present as pelvic mass. Pain may or may not be the complaint, but they generally present in early disease like in stage I and about 17% of the cases presents with bilateral involvement of ovaries with elevated CA125.[4] Five-year survival rate of stage III endometrioid ovarian carcinoma is 41%. Histologically, the glands look tubular similar to endometrium with squamous differentiation in 30-50% and luteinized stromal cells seen in 12% cases.[6]

Various aetiological determinants are thought to impact ovarian carcinoma. The most impactful ones are advanced age, genetic predisposition, and a family history of cancer. These factors are particularly related to continuous ovulation, hormonal changes, cumulative genetic damage, and chronic inflammation.[7-9] The exact mechanism by which malignant transformation in endometriosis occurs has not yet been demonstrated. However, Xiao et al reported that loss of BAF250a protein, up regulation in HNF-1β and loss of estrogen receptors are common in atypical endometriosis.

The precancerous cell must undergo several alterations in order for a tumor to develop. Such changes may have multiple underlying mechanisms, but one of the most

studied refers to oxidative stress, which may be associated with genetic abnormalities.

Current strategies to diagnose ovarian carcinoma include a medical history evaluation combined with the gynaecological exam, serum CA-125 quantification, and imaging tests (trans vaginal ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and or positron emission tomography (PET)), while also demanding a histopathological examination from either a diagnostic biopsy or, if possible, a surgical specimen for a definitive diagnosis and staging.[10-12]

Regarding the prognosis assessment, the FIGO stage, histologic subtype, grade, baseline serum CA-125 levels, the extent of debulking surgery, and chemotherapy schemes are traditionally deemed the most relevant independent prognostic factors of Ovarian carcinoma.[13,14] However, ongoing research has recently identified several molecular biomarkers associated with Ovarian carcinoma treatment response and prognosis, including mutations, gene expression patterns, and or epigenetic changes.[15-17]

The therapeutic management of ovarian carcinoma mainly relies on the disease stage, with tumour histology, molecular profile, and the patient's medical background also being relevant determinants. Traditionally, the front-line approach involves cytoreductive surgery followed by intravenous chemotherapy with platinum-containing drugs (cisplatin or carboplatin) typically combined with taxeme agents (paclitaxel and docetaxel) every 21 days for six cycles.

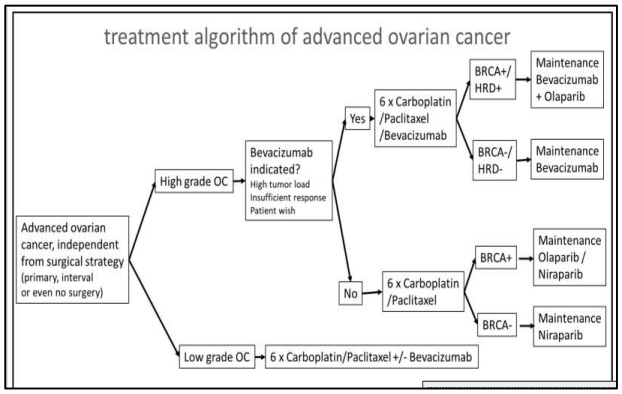

Figure 4: treatment algorithm for maintenance therapy of patients with advanced ovarian cancer based on clinical and molecular biological parameter.

Testing for a homologous recombination deficiency (HRD) in primary high-grade ovarian cancer is crucial for recommending the appropriate therapy. Patients with a BRCA germline mutation are defined as harbouring an HRD deficiency. However, there is a group of approximately 20% of patients without a BRCA mutation which harbour an HRD deficiency based on tumour genomic analyses. about 25% of the high grade endometrioid ovarian cancer were HRD positive (Figure 4).[18]

Although the majority of Ovarian carcinoma patients (80%) have a complete response after front-line treatment, over 60% of the patients with 1 cm of residual disease (suboptimal debulking) progress to around 18 months, often due to chemo resistance.[16,17,19-21] At a phase of disease recurrence, Ovarian carcinoma treatment commonly consists of second-line chemotherapy, which depends on platinum sensitivity. Based on the period between the completion of first-line platinum-based chemotherapy and disease recurrence (i.e., platinum-free interval (PFI)), Ovarian carcinoma can be classified as platinum-refractory (when it occurs during the first-line chemotherapy), resistant (within 6 months after treatment completion), partially sensitive (between 6 and 12 months) or highly sensitive (beyond 12 months).[22] Over the past few decades, a framework change has been observed, transition to a new phase with improved upfront interventions, such as hyper thermic intra peritoneal chemotherapy (HIPEC), to delay the disease's recurrence, reduce adverse effects and prolong patients' survival. HIPEC involves the intra peritoneal delivery of chemotherapeutic agents after cyto reductive surgery and under hyper thermic conditions to improve patients' outcomes by more effectively removing residual disease. This is partially due to hyperthermia, which increases the penetration of chemotherapeutic drugs at the peritoneal surface while enhancing the sensitivity of the tumour to treatment. These two factors, however, notably depend on the selected drug and the achieved temperature.[23,24] This evolution also encompasses broadening the treatment options to include more targeted approaches, namely the use of antiangiogenic agents, DNA damage repair-based therapeutics, hormone receptor modulators, and FRα-targeting drugs.[25]

Anti angiogenic Agents inhibit release of pro angiogenic factors, including VEGFA from the tumor, which can activate the proliferation of vascular endothelial cells, fuelling tumour neo angiogenesis. VEGFA and angiogenesis are crucial promoters of ovarian tumorigenesis. Both correlates directly with the disease's extent and inversely with Progression-free survival (PFS) and overall survival (OS), usually regardless of other prognostic determinants.[26]

DNA Damage Repair-Based therapeutic agents inhibit the activity of PARPs, which are proteins crucial for DNA damage repair. In malignancy, PARPs facilitate the repair of DNA damage, particularly single-strand breaks, which are induced by anti-neoplastic treatments. Tumour cells with a deficient homologous recombination repair (HRR) pathway, mainly due to mutations in BRCA1/2, are unable to repair DNA double-strand breaks. In these cells, PARPi have a negative effect, rendering the repair of DNA damage unfeasible. Consequently, these therapeutic agents promote the apoptosis of tumour cells through a process known as synthetic lethality.[16]

Hormone Receptor Modulators like Oestrogen is known to drive the proliferation of Ovarian carcinoma cells [26]. Oestrogen signalling is mediated by Oestrogen Receptor (ER)-alpha (ERα) and ER-beta (ERβ), each with different isoforms, which are further amplified by G protein-coupled oestrogen receptor 1 (GPER1) [27]. In vitro and in vivo studies show that oestrogen via ERα regulates ovarian carcinoma growth and promotes cell migration and epithelial–mesenchymal transition (EMT), influencing cell motility and survival. These modifications proceed through the down regulation of E-cadherin: a process that ERβ inhibits.[28] Indeed, ERβ, the most common ER form in normal ovary tissue, is thought to be an OC suppressor.[29]

While aromatase inhibitors block oestrogen synthesis, tamoxifen directly competes with oestrogen in order to bind to ER. Progesterone, gonadotropins, androgens, and the Gonadotropin-Releasing Hormone (GnRH) also play a role in the endocrine regulation of the ovary mediated by the hypothalamic–pituitary– ovary axis. While GnRH and progesterone seem protective against OC, gonadotropins, and androgens favour its progression.[30]s

FRα-Targeting Drugs The folate metabolism is essential in DNA synthesis, methylation, and repair.[31] The trans membrane glycoprotein FRα transports folic acid (folate) and its derivatives into cells via endocytosis. Most ovarian carcinomas over express FRα, while this receptor is absent in normal ovarian epithelium.[32] The synthesis of FRα is particularly common in advanced and high-grade serous endometroid Ovarian carcinoma, which is sustained even in recurrent diseases and within metastatic niches. Importantly, this receptor is reported to shed from the cell membrane into circulation. In endometroid Ovarian carcinoma patients, circulating receptor (sFRα) levels correlate with tumour FRα expression, disease burden, and treatment outcomes. Thus, sFRα might be an attractive biomarker of early EOC. Inclusively, this marker has exhibited higher accuracy than serum CA-125 levels.[33]

One of the emerging therapies for Ovarian carcinoma is cancer immunotherapy. This therapeutic method harnesses the power of the patient's immune system to eliminate the tumour. Numerous immune-based interventions have been approved to treat solid and haematologic tumours, including immune checkpoint inhibitors, nonspecific immune stimulation, adoptive cell therapy, and cancer vaccines. The involvement of the immune system in OC patients' outcomes is demonstrated by the observation that tumour-infiltrating lymphocytes and the lower expression of PD-L1 are associated with improved survival.[34]

Different gene therapy strategies have been explored for Ovarian carcinoma management in preclinical studies, including the replacement of tumour suppressor genes to restore cell control (e.g., TP53), oncogene inhibition strategies (e.g., EGFR), suicide gene therapy with the delivery of genes encoding for toxins (e.g., HSV-TK), genetic immunopotentiation to reinforce immune response against tumour cells (e.g., IL-12A/B), antiangiogenic gene therapy (e.g., COL18A1).

Drug repurposing (also known as drug re profiling, re-tasking, or repositioning) consists of identifying alternative uses for approved therapeutical agents that are outside the original prescription scope, even regarding non-cytotoxic drugs.[35] One of the repurposed drugs under investigation for Ovarian carcinoma management is vitamin D and its analogues.

In Ovarian carcinoma, the kinases involved in angiogenesis (e.g., VEGFRs), cell growth (e.g., EGFR), and intracellular signalling (e.g., PI3K/AKT/mTOR pathway) are reported to be over activated, being attractive therapeutic targets.[36] Numerous small-molecule kinase inhibitors have been evaluated in clinical trials for Ovarian carcinoma management.

Patients with ovarian tumours are commonly diagnosed with venous thrombo embolism (VTE), with an incidence ranging from 10 to 30%. This thrombotic event constitutes the second cause of death among oncological patients.[37] Importantly, even in the absence of VTE, most cancer patients present a state of blood hyper coagulation. Cumulative evidence suggests that underling this state, deregulated haemostatic components-endothelial cells, platelets, and coagulation/fibrinolysis systems-exhibit pro tumorigenic functions, including tumour cell growth, survival, proliferation, and invasion while also supporting cancer neo angiogenesis and metastatic dissemination.[36] Several haemostatic components have been suggested to play critical roles in OC progression. The overexpression of coagulation factor 3, commonly known as the tissue factor (TF), and the presence of tumour-educated platelets are some of the most studied mechanisms in this interface of VTE and Ovarian carcinoma progression.[36]

CONCLUSION

Endometrioid carcinoma ovary is usually associated with Endometriotic cyst ovary. In this case carcinoma developed even from remnant ovarian tissue with normal tumor markers. Patients with remnant ovarian tissue or ovary following hysterectomy or hysterectomy+ salpingoopherectomy, for any reason should be ideally followed up with 6 monthly ultrasound and tumour markers for early detection of ovarian pathologies. The prognosis of abovementioned patient would have been better if she followed up regularly. Hence contesting of HRD and BRCA1/2 germ line testing should be also aimed for in order to enable optimal and timely treatment decision on the maintenance therapy for patients in whom the HRD test will not be evaluable.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Paulose MK, Parambil NV, Kutty SP, Salahuddin S, Khalam MA, Jacob S. Endometrioid carcinoma arising from the remnant ovarian tissue. Int J Reprod Contracept Obstet Gynecol 2024;13:2940-6.