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BRCA-NEGATIVE HIGH-GRADE SEROUS OVARIAN CANCER WITH RECURRENT PROGRESSION: A CLINICAL CASE

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ABSTRACT

Introduction: *High-grade serous ovarian cancer (HGSOC) is characterized by pronounced genomic instability, frequent mutations in BRCA1/2 genes, and high clinical and molecular heterogeneity. In some patients, the disease is accompanied by a homologous recombination deficiency (HRD), which causes sensitivity to poly (ADP-ribose) polymerase (PARP) inhibitors. However, the efficacy of these drugs remains limited in BRCA wild-type patients.*

This study aimed to *analyze and describe a clinical case of BRCA-negative serous ovarian cancer complicated by multiple progressions and the formation of drug resistance.*

Methods: *This study presents a clinical case of a patient with a common form of HGSOC, without mutations in BRCA1/2 genes but with a moderately positive HRD status. Molecular genetic analysis was performed by next-generation sequencing using the Foundation Medicine platform. The effectiveness of the treatment was assessed through positron emission tomography combined with computed tomography, magnetic resonance imaging, and computed tomography, alongside serial measurements of the CA-125 tumor marker.*

Results: *The patient underwent cytoreductive surgery followed by five successive lines of chemotherapy, including platinum-based regimens, bevacizumab, liposomal doxorubicin, gemcitabine, and olaparib as a PARP inhibitor. Although transient partial responses were achieved, the disease subsequently progressed. Molecular genetic analysis confirmed the absence of BRCA1/2 mutations and revealed an HRD score of 20.1%, indicative of limited sensitivity to PARP inhibition. As the patient's general condition declined, a transition to palliative care was initiated in February 2025. The patient passed away in March 2025.*

Conclusions: *The presented case highlights the limited therapeutic possibilities in BRCA-negative HGSOC with moderate HRD status and demonstrates the need to develop new personalized treatment strategies in patients with an unfavorable molecular profile.*

Keywords: *high-grade serous ovarian cancer (HGSOC), BRCA-negative status, homologous recombination deficiency (HRD), PARP inhibitors, clinical case, chemotherapy, molecular profiling.*

Introduction: High-grade serous ovarian carcinoma (HGSOC) is the most common and aggressive histological subtype of epithelial ovarian cancer. This disease is characterized by pronounced genomic instability, a high frequency of somatic and germinal mutations, impaired *DNA* repair mechanisms, and activation of cellular stress signaling pathways. In most cases, the tumor develops against the background of molecular disorders in the TP53, *BRCA1/2 genes,* or other elements of the homologous recombination system. HGSOC is clinically characterized by an aggressive course, early intraperitoneal dissemination, and pronounced histological and molecular heterogeneity, complicating treatment response prediction and necessitating a personalized therapeutic approach [1, 2]. According to the international cancer registries, the median 5-year survival rate in patients with advanced HGSOC does not exceed 27%. This is significantly lower than in low-grade or early-stage tumors, where the survival rate can reach 70-90%. The main reasons for such unfavorable outcomes are late diagnosis, pronounced heterogeneity of the tumor, a tendency to rapid intraperitoneal spread, and the development of chemoresistance after the first courses of therapy [3,4]. According to molecular genetic studies, about 30-35% of HGSOCS are associated with disorders in the BRCA1 or BRCA2 genes, including germinal and somatic mutations and epigenetic inactivation, such as hypermethylation of promoter regions. These molecular defects lead to homologous recombination deficiency (HRD), forming the so-called HRD phenotype [5]. HRD is a central mechanism underlying genomic instability in epithelial ovarian cancer. It is associated with impaired high-precision repair of double-stranded DNA breaks. According to current molecular studies, signs of HRD are detected in approximately 50% of patients with HGSOC. This phenotype forms the therapeutic vulnerability of the tumor to poly (ADP-ribose) polymerase (PARP) inhibitors, whose action is based on the principle of synthetic lethality. In this regard, determining the HRD status is of key importance for choosing personalized therapy and evaluating the potential effectiveness of PARP inhibitors in this category of patients [6-8]. Poly inhibitors (ADP-ribose) polymerases (PARP) were initially developed as a maintenance therapy for patients with recurrent ovarian cancer who have achieved a complete or partial response to repeated chemotherapy with platinum preparations. Their clinical efficacy was convincingly demonstrated in three large, randomized phase III trials –

NOVA (ENGOT-OV16), SOLO-2 (ENGOT-OV21), and ARIEL3 – where there was a significant improvement in progression-free survival (PFS) compared to placebo. The results of these studies led to the approval of niraparib, olaparib, and rukaparib as maintenance therapy for recurrent platinum-sensitive ovarian cancer, regardless of the presence of mutations in *BRCA1/2* or other biomarkers. This expanded the indications for using PARP inhibitors and confirmed their role as one of the key components of a personalized approach to treating recurrent tumors [9, 10].

This study aimed to analyze and describe a clinical case of *BRCA*-negative serous ovarian cancer complicated by multiple progressions and the formation of drug resistance.

Materials and methods: This paper presents a clinical case of a patient with a common form of HGSOC under observation at the Almaty Cancer Center. An integrated approach was used to assess the molecular and immunohistochemical profile of the tumor.

A next-generation molecular genetic sequencing (NGS) study was performed in Foundation Medicine Inc.'s (USA) laboratory to assess the mutation status. The test evaluated mutations in the BRCA1/2 genes and the level of genomic instability (HRD), which revealed the absence of BRCA mutations and the HRD status of 20.1%.

An immunohistochemical study of the tumor tissue was performed using antibodies to the WT1, PAX8, p53, p16, Ki-67 markers, estrogen and progesterone receptors (ER/PR), and the folate α receptor. The study was performed on the VENTANA BenchMark ULTRA (Roche) platform using the BN3.2 monoclonal antibody (Novocastra/Leica). Mutation-specific overexpression of p53 and Ki-67 at 30% and moderate and strong expression of folate receptor α in 35% of tumor cells were found. Expression of ER and PR was absent.

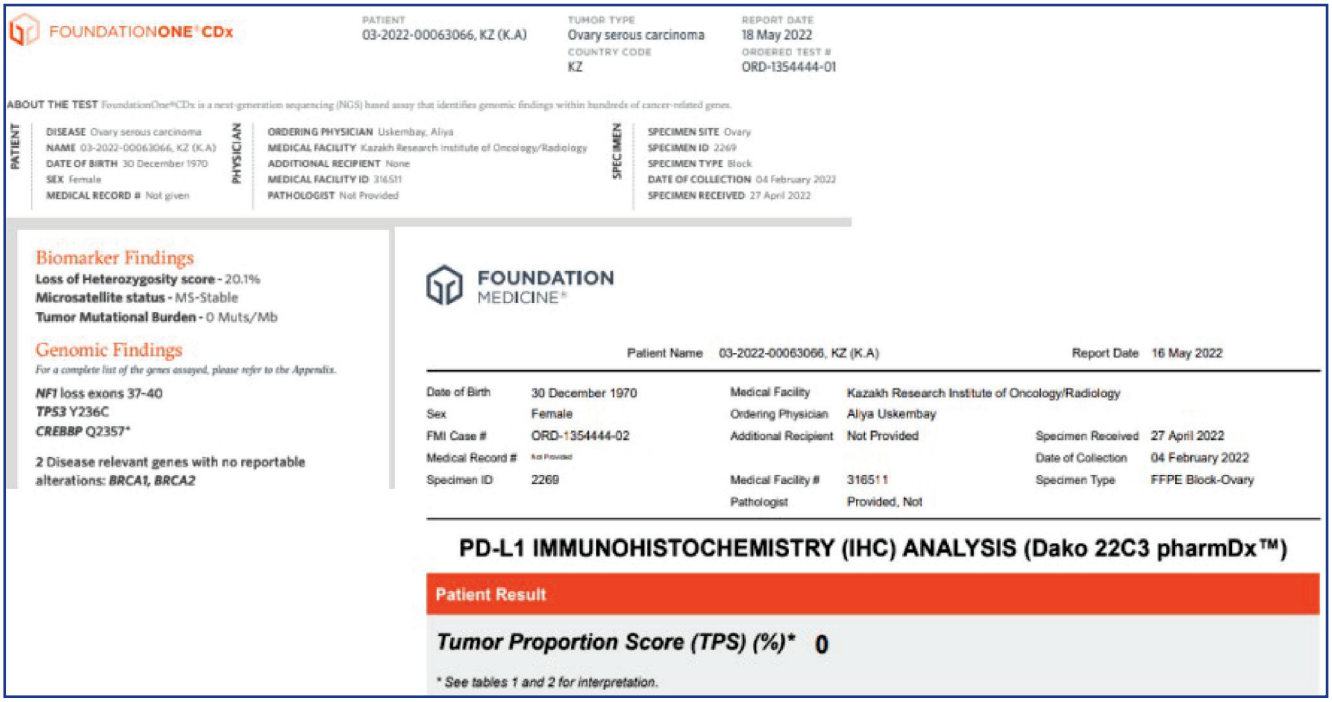
In contrast to the clinical case described in our previous article [11], which documented a rare *BRCA1* mutation *(p.181T>G; p.Cys61Gly)* associated with prolonged tumor stabilization exceeding three years, this patient had no *BRCA1/2* mutations and an HRD score of 20.1%, indicating limited expected benefit from PARP inhibitor therapy. Variations in the molecular profile proved to be critical determinants in selecting therapeutic strategies, prognostication of treatment response, and prediction of disease trajectory. Disease progression and therapeutic response were dynamically monitored through serial imaging studies, including magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography/computed tomography (PET/CT), complemented by sequential measurements of serum CA-125 levels.

Clinical case:

Patient Information: Patient A. was 42 years old at the diagnosis. She presented in February 2022 with clinical signs necessitating immediate surgical intervention. Primary cytoreductive surgery was performed with an extensive surgical approach, including total abdominal hysterectomy with bilateral salpingo-oophorectomy, resection of the round ligament of the liver, excision of a tumor mass from the left paracolic gutter, total omentectomy, and pelvic and para-aortic lymph node dissection. Histological analysis confirmed HGSOC, FIGO stage IIIC (pT3C pN1c M0).

Between March and June 2022, the patient received six cycles of chemotherapy consisting of carboplatin (AUC 5) and paclitaxel (175 mg/m^2), administered intravenously every 21 days. A favorable treatment response was observed, as evidenced by a decline in the CA-125 tumor marker level to 32 U/mL by July 2022.

In June 2022, the tumor molecular genetic profiling was done by NGS using Foundation Medicine Inc. USA). No pathogenic variants were identified in the *BRCA1/2 genes*, indicating a *BRCA wild-type status*. The HRD score of 20.1% evidenced moderate genomic instability and suggested limited sensitivity to PARP inhibitor therapy (Figure 1).


FOUNDATIONONE® CDx

PATIENT 03-2022-00063066, KZ (K.A)
TUMOR TYPE Ovary serous carcinoma
COUNTRY CODE KZ
REPORT DATE 18 May 2022
ORDERED TEST # ORD-1354444-01

ABOUT THE TEST FoundationOne®CDx is a next-generation sequencing (NGS) based assay that identifies genomic findings within hundreds of cancer-related genes.

PATIENT
DISEASE Ovary serous carcinoma
NAME 03-2022-00063066, KZ (K.A)
DATE OF BIRTH 30 December 1970
SEX Female
MEDICAL RECORD # Not given

PHYSICIAN
ORDERING PHYSICIAN Uskembay, Aliya
MEDICAL FACILITY Kazakh Research Institute of Oncology/Radiology
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 316511
PATHOLOGIST Not Provided

SPECIMEN
SPECIMEN SITE Ovary
SPECIMEN ID 2269
SPECIMEN TYPE Block
DATE OF COLLECTION 04 February 2022
SPECIMEN RECEIVED 27 April 2022

Biomarker Findings
Loss of Heterozygosity score - 20.1%
Microsatellite status - MS-Stable
Tumor Mutational Burden - 0 Muts/Mb

Genomic Findings
For a complete list of the genes assayed, please refer to the Appendix.
NF1 loss exons 37-40
TP53 Y236C
CREBBP Q2357*

2 Disease relevant genes with no reportable alterations: ***BRCA1, BRCA2***

FOUNDATION MEDICINE®

Patient Name 03-2022-00063066, KZ (K.A) Report Date 16 May 2022

Date of Birth	30 December 1970	Medical Facility	Kazakh Research Institute of Oncology/Radiology		
Sex	Female	Ordering Physician	Aliya Uskembay		
FMI Case #	ORD-1354444-02	Additional Recipient	Not Provided	Specimen Received	27 April 2022
Medical Record #	Not Provided			Date of Collection	04 February 2022
Specimen ID	2269	Medical Facility #	316511	Specimen Type	FFPE Block-Ovary
		Pathologist	Provided, Not		

PD-L1 IMMUNOHISTOCHEMISTRY (IHC) ANALYSIS (Dako 22C3 pharmDx™)

Patient Result

Tumor Proportion Score (TPS) (%)* **0**

** See tables 1 and 2 for interpretation.*

Figure 1 – Molecular genetic and immunohistochemical analysis was performed using next-generation sequencing (FoundationOne® CDx, Foundation Medicine, Cambridge, USA)

An immunohistochemical study of the tumor was also performed at the Charité University Hospital (Berlin, Germany). Mutational type of p53 expression, Ki-67 proliferative activity index at the level of 30%, expression of folate receptor α in 35% of tumor cells, and negative expression of hormone receptors ER and PR were found.

To evaluate the disease extent, a PET/CT scan performed in February 2022 revealed increased metabolic activity in the mesenteric lymph nodes (SUVmax 3.8–6.1). Follow-up imaging in November 2022 showed no evidence of disease recurrence (Figure 2).

In December 2022, the clinical case was reviewed during a multidisciplinary consultation at the Kazakh Institute of Oncology and Radiology, with the participation of specialists from Charité University Hospital. Considering the absence of disease recurrence on the PET/CT scan from November 2022 and a platinum-free interval exceeding six months, the patient was classified as platinum-sensitive. Based on the results of the discussion, repeated platinum-containing chemotherapy in combination with bevacizumab is recommended, followed by the appointment of a PARP inhibitor when the disease stabilizes.

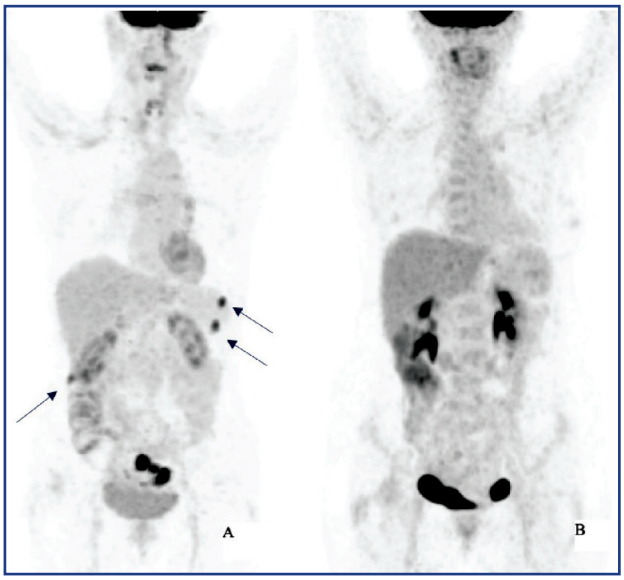


Figure 2 – PET/CT scan: A – an increased metabolic activity in the abdominal lymph nodes (arrows), consistent with active disease (February 2022); B – a marked reduction in metabolic activity of previously hypermetabolic lymph nodes (November 2022)

From April to September 2023, the patient underwent six cycles of second-line chemotherapy consisting of carboplatin (AUC 5), paclitaxel (175 mg/m^2), and bevacizumab (15 mg/kg), administered intravenously every 21 days. The treatment was well tolerated. A positive treatment response was observed, reducing the CA-125 tumor marker level from 115 to 48 U/mL. Follow-up PET/CT imaging in August 2023 demonstrated decreased metabolic activity in the previously affected lymph nodes, consistent with a partial metabolic response (Figure 3).

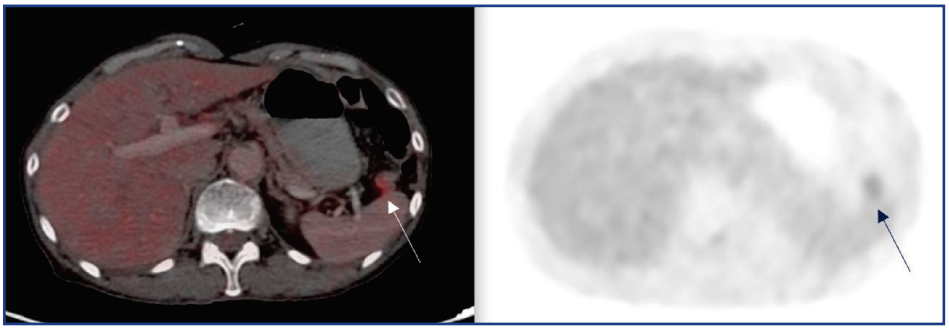


Figure 3 – A PET/CT scan from August 2023: reduced metabolic activity in the affected lymph nodes (arrows) indicates a favorable response to second-line chemotherapy

From October 2023 to February 2024, the patient received maintenance therapy with olaparib at a dose of 300 mg twice daily. This regimen was initiated following a favorable response to second-line treatment and was in alignment with international guidelines for the use of PARP inhibitors in patients with platinum-sensitive disease despite the absence of *BRCA* mutations. However, in March 2024, both biochemical and radiological evidence of disease progression was observed: CA-125 levels increased to 151 U/mL, and PET/CT imaging revealed new metabolically active lesions in the cervical, mediastinal, para-aortic, mesenteric, and paracaval lymph nodes, as well as radiophar-

maceutical uptake in the skin of the neck and the anterior abdominal wall (Figure 4).

From April to June 2024, the patient received chemotherapy consisting of paclitaxel at a dose of 160 mg administered intravenously on days 1, 8, and 15 of each 21-day cycle, in combination with bevacizumab 15 mg/kg every 21 days. A total of three cycles were completed. During treatment, the patient developed grade 2 leukopenia. A PET/CT scan performed in July 2024 revealed signs of peritoneal carcinomatosis, ascites, and enlargement of the mesenteric and para-aortic lymph nodes, along with cystic lesions in the liver suspected to be of metastatic origin.

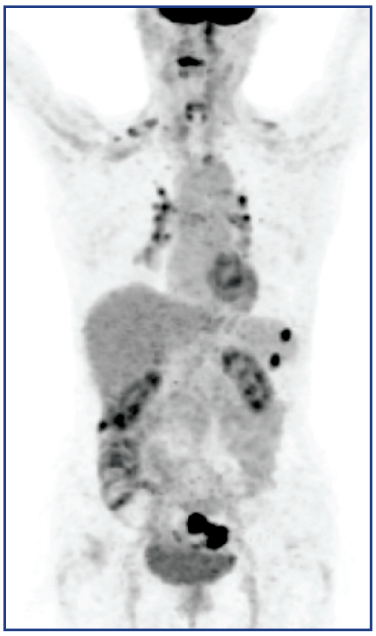


Figure 4 – PET/CT image: New metabolically active lesions in the lymph nodes, the skin of the neck, and the abdominal wall

From July to October 2024, the patient received sequential chemotherapy with continued use of bevacizumab. Two cycles of liposomal doxorubicin (40 mg/m2 intravenously) with bevacizumab (15 mg/kg) were initially administered. Due to the absence of clinical or biochemical improvement, the treatment regimen was modified to include three cycles of gemcitabine (1000 mg/m^2 on days 1 and 8 of each 21-day cycle), again combined with bevacizumab at the same dosage. Despite these interventions, no objective treatment response was achieved. PET/CT and MRI scans performed in October 2024 revealed multiple metastatic lesions in the liver and peritoneum (Figure 5), as well as bilateral pleural effusions.

A CT scan performed in February 2025 confirmed intestinal obstruction, multiple hepatic metastases, and bilateral pleural effusions. Due to progressive clinical deterioration, the patient underwent laparotomy, followed by a relaparotomy with gastrostomy and cecostomy. At that time, the CA-125 level exceeded 1100 U/mL, and the patient's performance status was assessed as ECOG 3. In light of the lack of therapeutic response, the extensive progression of the disease, and the overall decline in clinical condition, a decision was made in February 2025 to transition the patient to palliative care. Despite supportive measures, the patient succumbed to disease progression in March 2025.

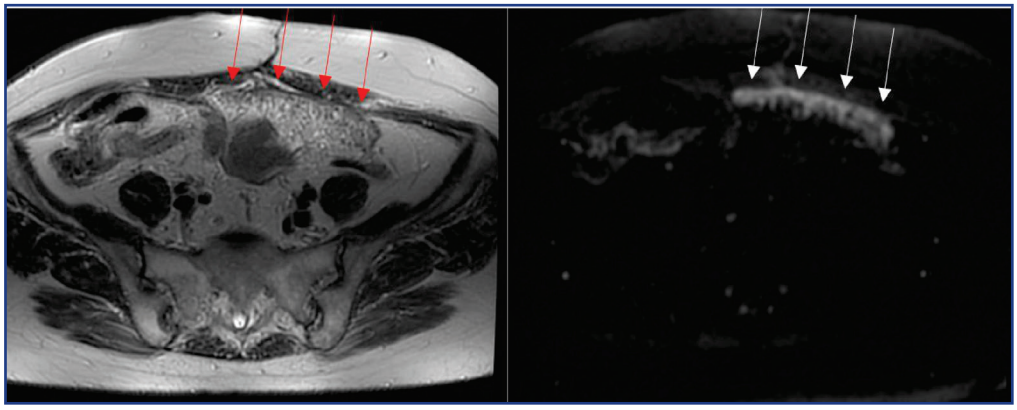


Figure 5 – Axial pelvic MRI: Signs of peritoneal carcinomatosis. The T2-weighted image (left) and diffusion-weighted image (right) reveal irregular thickening and nodularity along the peritoneal surfaces (arrows), consistent with metastatic peritoneal involvement

Results: The patient underwent complex treatment, including cytoreductive surgery, five lines of chemotherapy, targeted therapy, and maintenance treatment with a PARP inhibitor. After the first line of chemotherapy, partial remission was achieved with a biochemical decrease in CA-125 levels to 32 U/ml. PET/CT from November 2022 showed no signs of relapse. Considering the platinum sensitivity (over more than 6 months), repeated platinum-containing chemotherapy in combination with bevacizumab was started in April 2023. At the end of six cycles, partial metabolic remission was achieved, and the CA-125 level decreased to 48 U/ml. Since October 2023, maintenance therapy with olaparib was performed, but by March 2024, biochemical and visual progression was recorded: an increase in CA-125 to 151 U/ml and the detection of active metastatic lymph nodes. Due to documented disease progression, treatment with weekly paclitaxel in combination with bevacizumab was initiated between April and June 2024. However, follow-up PET/CT imaging revealed continued disease spread. Subsequent chemotherapy regimens incorporating liposomal doxorubicin and gemcitabine likewise failed to elicit an objective response. Trends in CA-125 levels throughout treatment, showing initial response followed by progressive elevation during later lines of therapy and transition to palliative care (Figure 6), and PET/CT imaging from October 2024 demonstrated multiple metastatic lesions. NGS revealed no pathogenic mutations in *BRCA1/2* and HRD score of 20.1%, indicative of moderate genomic instability and limited expected benefit from PARP inhibitor therapy. Due to disease progression and functional decline (ECOG performance status 3), the patient was transitioned to palliative care in February 2025. A fatal outcome was recorded in March 2025 (Table 1).

The timeline of this clinical case is provided in Table 1.

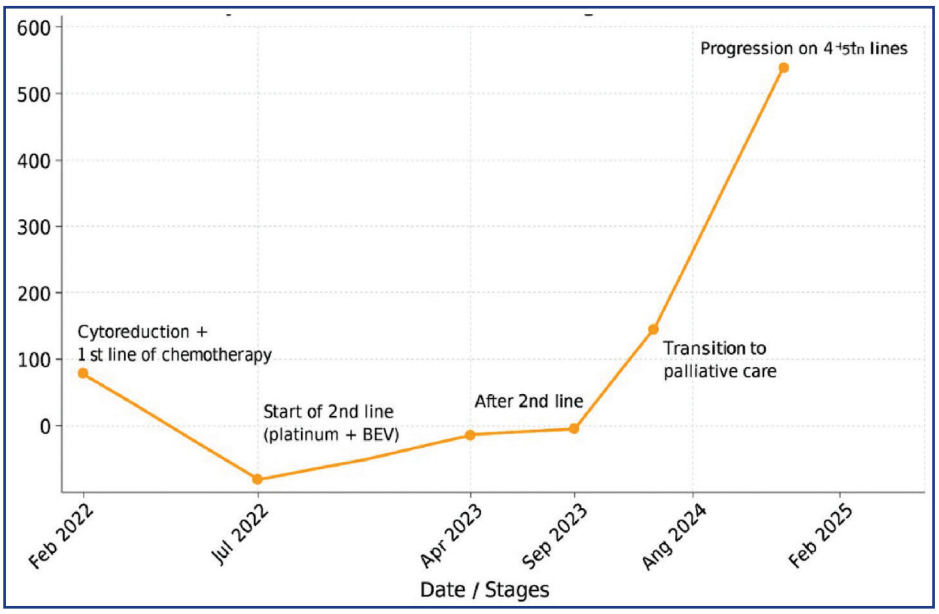


Figure 6 – Changes in CA-125 levels during treatment

Table 1 – Timeline of the clinical case of *BRCA*-negative serous ovarian cancer with multiple progressions and drug resistance

Date	Event
February 2022	Initial presentation and primary cytoreductive surgery. Diagnosis: HGSOC, FIGO IIIC.
March - June 2022	First-line chemotherapy (carboplatin + paclitaxel), favorable response (CA-125 decrease to 32 U/mL).
June 2022	NGS: BRCA-negative, HRD 20.1% confirmed.
November 2022	PET/CT: No signs of recurrence.
April - September 2023	Second-line chemotherapy (carboplatin + paclitaxel + bevacizumab): partial metabolic response, CA-125 decreased to 48 U/mL.
October 2023 - February 2024	Maintenance therapy with olaparib.
March 2024	A progression was detected: CA-125 increased to 151 U/mL; new metastatic lesions on PET/CT.
April - June 2024	Third-line chemotherapy (weekly paclitaxel + bevacizumab): the progression continued.
July - October 2024	Fourth-line chemotherapy: liposomal doxorubicin + bevacizumab; switch to gemcitabine + bevacizumab; no response.
October 2024	MRI and PET/CT: Liver metastases, peritoneal carcinomatosis, pleural effusion.
February 2025	Intestinal obstruction: palliative surgeries (gastrostomy, cecostomy); ECOG 3; transition to palliative care.
March 2025	Patient deceased.

Discussion: The presented clinical case illustrates the course of FIGO IIIC HGSOC in a *BRCA-negative* patient with moderate genomic instability. Despite complete cytoreductive surgery, two consecutive platinum regimens, targeted therapy with bevacizumab, and maintenance treatment with olaparib, the disease was char-

acterized by a progressive and resistant course [12]. In contrast to the clinical case presented in a previously published paper [11], where the detection of a rare *BRCA1 gene* mutation (p.181T>G; p. Cys61Gly) allowed us to achieve long-term stabilization of the tumor process for more than three years on the background of PARP-inhibitor therapy; in our case, the molecular profile was different [13].

The patient had no mutations in the BRCA1/2 genes, and the HRD level was 20.1%, indicating a limited sensitivity to PARP inhibitors. Despite similar maintenance therapy with olaparib, the effect was short-lived, and disease progression was recorded [14]. This highlights the importance of molecular profiling in the early management of patients with epithelial ovarian tumors. In addition, high p53 expression, absence of ER/PR receptors, and moderate folate α receptor expression (35%) reflect the aggressive molecular phenotype of the tumor.

Repeated changes in chemotherapy regimens, including liposomal doxorubicin, gemcitabine, and weekly paclitaxel, did not provide a stable response. These lines' lack of clinical efficacy highlights the limitations of available treatment strategies in patients with an unfavorable molecular profile. In conditions of aggressive course and cumulative toxicity, timely transition to palliative care plays a key role.

Conclusions: The presented clinical case of HGDOC, FIGO stage IIIC, in a *BRCA-negative* patient with moderate genomic instability (an HRD score of 20.1%) illustrates an aggressive disease course with limited response to multi-line therapy. Despite optimal primary cytoreduction, sequential platinum-based chemotherapy, and targeted antiangiogenic therapy, the patient experienced recurrent relapses and multiple episodes of disease progression. The absence of *BRCA1/2 mutations* and a borderline HRD score likely contributed to reduced sensitivity to PARP inhibition and the lack of durable treatment response. This case highlights the urgent need to develop novel individualized treatment strategies and identify additional therapeutic targets in patients with unfavorable molecular profiles. Emphasis should be placed on early detection of resistance predictors and the implementation of truly personalized oncologic care tailored to the genetic and phenotypic characteristics of the tumor.

References

1. Vázquez-García I., Uhlitz F., Ceglia N., Lim JL.P., Wu M., Mohibullah N., Niyazov J., Ruiz AE.B., Boehm K.M., Bojilova V., Fong C.J., Funnell T., Grewal D., Havasov E., Leung S., Pasha A., Patel D.M., Pourmaleki M., Rusk N., Shi H., Vanguri R., Williams M.J., Zhang A.W., Broach V., Chi D.S., Da Cruz Paula A., Gardner G.J., Kim S.H., Lennon M., Long Roche K., Sonoda Y., Zivanovic O., Kundra R., Viale A., Derakhshan F.N., Geneslaw L., Issa Bhaloo S., Maroldi A., Nunez R., Pareja F., Stylianou A., Vahdatinia M., Bykov Y., Grisham R.N., Liu Y.L., Lakhman Y., Nikolovski I., Kelly D., Gao J., Schietinger A., Hollmann T.J., Bakhoum S.F., Soslow R.A., Ellenson L.H., Abu-Rustum N.R., Aghajanian C., Friedman C.F., McPherson A., Weigelt B., Zamarin D., Shah S.P. Ovarian cancer mutational processes drive site-specific immune evasion // Nature. – 2022. – Vol. 612(7941). – P. 778-786. https://doi.org/10.1038/s41586-022-05496-1

2. Deng Y., Tan Y., Zhou D., Bai Y., Cao T., Zhong C., Huang W., Ou Y., Guo L., Liu Q., Yin D., Chen L., Luo X., Sun D., Sheng X. Single-Cell RNA-Sequencing Atlas Reveals the Tumor Microenvironment of Metastatic High-Grade Serous Ovarian Carcinoma // Frontiers in Immunology. – 2022. – Vol. 13. – Art. No. 923194. https://doi.org/10.3389/fimmu.2022.923194

3. Zhang X., Hong S., Yu C., Shen X., Sun F., Yang J. Comparative analysis between high-grade serous ovarian cancer and healthy ovarian tissues using single-cell RNA sequencing // Frontiers in Oncology. – 2023. – Vol. 13. – Art. No. 1148628. https://doi.org/10.3389/fonc.2023.1148628

4. Qiu J., Ren T., Liu Q., Jiang Q., Wu T., Cheng L.C., Yan W., Qu X., Han X., Hua K. Dissecting the Distinct Tumor Microenvironments of HRD and HRP Ovarian Cancer: Implications for Targeted Therapies to Overcome PARPi Resistance in HRD Tumors and Refractoriness in HRP Tumors // Advanced Science. – 2024. – Vol. 11 (38). – Art. No. e2309755. https://doi.org/10.1002/advs.202309755

5. Perrone E., Tudisco R., Pafundi P.C., Guido D., Ciucci A., Martinelli E., Zannoni G.F., Piermattei A., Spadola S., Ferrante G., Marchetti C., Scambia G., Fagotti A., Gallo D. What's beyond BRCA Mutational Status in High Grade Serous Ovarian Cancer? The Impact of Hormone Receptor Expression in a Large BRCA-Profiled Ovarian Cancer Patient Series: A Retrospective Cohort Study // Cancers (Basel). – 2022. – Vol. 14 (19). – Art. No. 4588. https://doi.org/10.3390/cancers14194588

6. Luo Y., Xia Y., Liu D., Li X., Li H., Liu J., Zhou D., Dong Y., Li X., Qian Y., Xu C., Tao K., Li G., Pan W., Zhong Q., Liu X., Xu S., Wang Z., Liu R., Zhang W., Shan W., Fang T., Wang S., Peng Z., Jin P., Jin N., Shi S., Chen Y., Wang M., Jiao X., Luo M., Gong W., Wang Y., Yao Y., Zhao Y., Huang X., Ji X., He Z., Zhao G., Liu R., Wu M., Chen G., Hong L.; COCPO Consortium., Ma D., Fang Y., Liang H., Gao Q. Neoadjuvant PARPi or chemotherapy in ovarian cancer informs targeting effector Treg cells for homologous-recombination-deficient tumors // Cell. – 2024. – Vol. 187(18). – P. 4905-4925.e24. https://doi.org/10.1016/j.cell.2024.06.013

7. Planas-Paz L., Pauli C. Leveraging homologous recombination deficiency for sarcoma: Unravelling homologous recombination repair deficiency and therapeutic opportunities in soft tissue and bone sarcoma // Pathologie (Heidelb). – 2024. – P. 14-19. https://doi.org/10.1007/s00292-024-01381-y

8. Xiao Y., Wu Y., Wang Q., Li M., Deng C., Gu X. Repression of PFKFB3 sensitizes ovarian cancer to PARP inhibitors by impairing homologous recombination repair // Cell Comm. Signal. – 2025. – Vol. 23(1). – Art. No. 48. (https://doi.org/10.1186/s12964-025-02056-8

9. Mirza M.R., Coleman R.L., González-Martín A., Moore K.N., Colombo N., Ray-Coquard I., Pignata S. The forefront of ovarian cancer therapy: update on PARP inhibitors // Ann. Oncol. – 2020. – Vol. 31(9). – P. 1148-1159. https://doi.org/10.1016/j.annonc.2020.06.004

10. González-Martín A., Desauw C., Heitz F., Cropet C., Gargiulo P., Berger R., Ochi H., Vergote I., Colombo N., Mirza M.R., Tazi Y., Canzler U., Zamagni C., Guerra-Alia E.M., Levaché C.B., Marmé F., Bazan F., de Gregorio N., Dohollou N., Fasching P.A., Scambia G., Rubio-Pérez M.J., Milenkova T., Costan C., Pautier P., Ray-Coquard I., PAOLA1/ENGOT-ov25 investigators. Maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced high-grade ovarian cancer: Main analysis of second progression-free survival in the phase III PAOLA-1/ENGOT-ov25 trial // Eur. J. Cancer. – 2022. – Vol. 174. – P. 221-231. https://doi.org/10.1016/j.ejca.2022.07.022

11. Aidarov A.E., Khaidarov S., Kaidarova D.R., Bolatbekova R.O., Aidarov D.E., Amankulov Zh.M., Orazgaliyeva M.G., Ossikbayeva S.O. BRCA-associated ovarian cancer: Experience in personalized treatment. A clinical case // Oncol. Radiol. Kazakhstan. – 2025. – Vol. 1 (75). – P. 75-81. https://doi.org/10.52532/2521-6414-2025-1-75-419

12. Kim S.I., Lee M., Kim H.S., Chung H.H., Kim J.W., Park N.H., Song Y.S. Effect of BRCA mutational status on survival outcome in advanced-stage high-grade serous ovarian cancer // J. Ovar. Res. – 2019. – Vol. 12(1). – Art. No. 40. https://doi.org/10.1186/s13048-019-0511-7

13. Birgisdóttira A., Myklebustc T.A, Bjørnslette M., Rognlienf V.W., Paulsena T., Døruma A. BRCA mutation testing and association with oncologic outcome and incidence of ovarian cancer in Norway // Int. J. Gynecol. Cancer. – 2024. – Vol. 35 (2). – Art. No. 100029. https://doi.org/10.1016/j.ijgc.2024.100029

14. Gai M., Zhao L., Li H., Jin G., Li W., Wang F., Liu M. LCP1 promotes ovarian cancer cell resistance to olaparib by activating the JAK2/STAT3 signalling pathway // Cancer Biol. Ther. – 2024. – Vol. 25 (1). – Art. No. 2432117. https://doi.org/10.1080/15384047.2024.2432117

АҢДАТПА

BRCA-ТЕРІС АНАЛЫҚ БЕЗДІҢ ЖОҒАРЫ ДӘРЕЖЕЛІ СЕРОЗДЫ ҚАТЕРЛІ ІСІГІ, ҚАЙТАЛАНАТЫН ҮДЕУІ: КЛИНИКАЛЫҚ ЖАҒДАЙДЫ

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Өзектілігі: *Аналық бездің жоғары дәрежелі серозды қатерлі ісігі (HGSOC) айқын геномдық тұрақсыздықпен, BRCA1/2 гендеріндегі жиі мутациялармен және жоғары клиникалық және молекулалық гетерогенділікпен сипатталады. Кейбір науқастарда ауру гомологиялық рекомбинацияның (HRD) жетіспеушілігімен бірге жүреді, бұл PARP ингибиторларына сезімталдықты тудырады. Алайда, Бұл препараттардың BRCA-жабайы түрі ісіктердегі тиімділігі шектеулі болып қалады.*

Зерттеу мақсаты *– бірнеше үдеумен және дәріге төзімділіктің қалыптасуымен асқынған BRCA-теріс аналық бездің серозды қатерлі ісігі бар науқасты емдеудің клиникалық жағдайын талдау және сипаттау.*

Әдістер: *Бұл зерттеу BRCA1/2 гендерінде мутациясы жоқ, бірақ орташа оң HRD мәртебесі бар HGSOC жалпы формасы бар науқастың клиникалық жағдайын ұсынады. Молекулалық-генетикалық талдау Foundation Medicine платформасында келесі ұрпақ секвенциясы арқылы жүргізілді. Емдеудің тиімділігі CA-125 ісік маркерін сериялық өлшеумен қатар компьютерлік томографиямен біріктірілген позитронды-эмиссиялық томография, магниттi резонансты томография және компьютерлік томография арқылы бағаланды.*

Нәтижелері: *Науқас циторедуктивті операциядан өтті, содан кейін платина негізіндегі режимдерді, бевацизумабты, липосомалық доксорубицинді, гемцитабинді және поли(АДФ-рибоза) полимераза (ПАРП) ингибиторлары олапарибті қоса алғанда, химиотерапияның қатарынан бес бағыты жүргізілді. Өтпелі ішінара реакцияларға қол жеткізілгенімен, кейіннен ауру асқынып кетті. Молекулалық-генетикалық талдау BRCA1/2 мутацияларының жоқтығын растады және HRD 20,1% көрсеткішін анықтады, Бұл ПАРП тежелуіне шектеулі сезімталдықты көрсетеді. Науқастың жалпы жағдайы нашарлағандықтан, 2025 жылдың ақпанында паллиативтік көмекке көшу басталды. Науқас 2025 жылдың наурыз айында қайтыс болды.*

Қорытынды: *Ұсынылған жағдай орташа HRD мәртебесі бар BRCA-теріс HGSOC препараттарының шектеулі емдік мүмкіндіктерін көрсетеді және қолайсыз молекулалық профилі бар науқастарды емдеудің жаңа жекелендірілген стратегияларын әзірлеу қажеттілігін көрсетеді.*

Түйін сөздер: *аналық бездің жоғары дәрежелі серозды қатерлі ісігі (HGSOC), BRCA-теріс статусы, гомологиялық рекомбинация тапшылығы (HRD), ПАРП ингибиторлары, клиникалық жағдайы, химиотерапия, молекулалық профильдеу.*

АННОТАЦИЯ

BRCA-НЕГАТИВНЫЙ СЕРОЗНЫЙ РАК ЯИЧНИКОВ ВЫСОКОЙ СТЕПЕНИ ЗЛОКАЧЕСТВЕННОСТИ С РЕЦИДИВИРУЮЩИМ ПРОГРЕССИРОВАНИЕМ: КЛИНИЧЕСКИЙ СЛУЧАЙ

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Актуальность: *Серозный рак яичников высокой степени злокачественности (high-grade serous ovarian cancer, HGSOC) характеризуется выраженной нестабильностью генома, частыми мутациями в генах BRCA1/2 и высокой клинической и молекулярной гетерогенностью. У некоторых пациентов заболевание сопровождается дефицитом гомологичной рекомбинации (homologous recombination deficiency, HRD), что обуславливает чувствительность к ингибиторам поли(АДФ-рибозо)полимеразы (ПАРП). Однако эффективность этих препаратов при BRCA дикого типа остается ограниченной.*

Цель исследования *– проанализировать и описать клинический случай лечения пациентки с BRCA-негативным серозным раком яичников, осложненным множественными прогрессиями и формированием лекарственной устойчивости.*

Методы: *В данной публикации представлен клинический случай пациента с распространенной формой HGSOC, без мутаций в генах BRCA1/2, но с умеренно положительным статусом HRD. Молекулярно-генетический анализ проводился с использованием секвенирования нового поколения на платформе Foundation Medicine. Эффективность лечения оценивалась с помощью позитронно-эмиссионной томографии в сочетании с компьютерной томографией, магнитно-резонансной томографии, компьютерной томографии, а также последовательных измерений опухолевого маркера CA-125.*

Результаты: *Пациентке была проведена циторедуктивная операция, за которой последовали пять последовательных курсов химиотерапии, включая схемы на основе платины, бевацизумаб, липосомальный доксорубицин, гемцитабин и ингибитор ПАРП олапариб. Хотя были достигнуты временные частичные ответы, впоследствии заболевание прогрессировало. Молекулярно-генетический анализ подтвердил отсутствие мутаций BRCA1/2 и выявил дефицит гомологичной рекомбинации (HRD), который составил 20,1%, что указывает на ограниченную чувствительность к ингибированию ПАРП. Поскольку общее состояние пациента ухудшилось, в феврале 2025 года был начат переход на паллиативную помощь. Пациент скончался в марте 2025 года.*

Заключение: *Представленный случай подчеркивает ограниченные терапевтические возможности при BRCA-негативном HGSOC с умеренным HRD статусом и демонстрирует необходимость разработки новых персонализированных стратегий лечения пациентов с неблагоприятным молекулярным профилем.*

Ключевые слова: *серозный рак яичников высокой степени злокачественности (HGSOC), BRCA-негативный статус, дефицит гомологичной рекомбинации (HRD), ингибиторы поли(АДФ-рибозо)полимеразы (ПАРП), клинический случай, химиотерапия, молекулярное профилирование.*

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