International Journal of
Clinical Images and Medical Reviews

*Case Report*

# Hereditary breast ovarian cancer syndrome: One case, multiple lessons

**Ikram Burney**
Senior Consultant, Medicine, Oman.

**Abstract**

Ovarian cancer is one the most common gynecological cancers, and epithelial ovarian cancer is the commonest sub-type. Between 10 and 15% of all epithelial ovarian cancers occur secondary to a mutation in *BRCA1* or *BRCA2* gene, and may be associated with breast cancer, known as hereditary breast ovarian cancer syndrome (HBOCS). We report a case of HBOCS, highlight the importance of family history and treatment history and discuss the recent developments in surgery and systemic treatment for patients in relation to the presentation of this case.

## Introduction

Ovarian cancer is one the most common gynecological cancers [1] Epithelial ovarian cancer is the commonest sub-type [2]. Between 10 and 15% of all ovarian cancers occur secondary to a mutation in a cancer susceptibility gene [3]. Mutations in BRCA1 and BRCA2 gene are the commonest cause of hereditary ovarian cancer [4, 5]. These mutations also predispose the individuals to other cancers. Patients with epithelial ovarian cancer may also develop breast cancer [6]. We report one such case here, and discuss the recent advances in the medical and surgical management of hereditary breast ovarian cancer syndrome (HBOCS).

## Case History

A 57 year-old lady presented with abnormal vaginal bleeding and abdominal distention. She was diagnosed to have high grade ovarian cancer, underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy and omentectomy, and was found to have stage IIIC serous papillary type of high grade ovarian cancer. The patient was treated with 6 cycles of Carboplatin and Paclitaxel to complete serological and radiological remission, however, she tolerated the chemotherapy with frequent episodes of febrile neutropenia. Three years later, the disease relapsed and the patient was treated with 6 cycles of Liposomal Doxorubicin to state of complete serological remission. One year later, the disease relapsed yet again, and this time, she received Carboplatin as a single agent. The disease entered serological remission after 3 cycles, however, the patient could not continue treatment because of repeated febrile neutropenia and thrombocytopenia

One year later, the disease relapsed a 3rd time. CT scan showed disease only at one site (**Figure 1a**) and the patient was treated with Carboplatin at a reduced dose, once again to a state of complete serological and radiological remission (**Figure 1b**). A surveillance mammogram was reported as BIRADS II and the bone mineral density revealed osteopenia. One year later, the disease relapsed a 4th time, again in a solitary site, and the patient was counseled about treatment with chemotherapy followed by a secondary cyto-reductive surgery, to which the patient agreed. The patient received 6 cycles of chemotherapy at reduced doses, followed by surgery. There was no residual disease and the patient remained in complete remission for more than one year and 3 months.

At this stage the CA-125 was seen to rise again serially, and mammogram showed a 2.2 cm speculated lesion in the left breast. A fine needle aspiration was highly suggestive of breast cancer, and a core biopsy revealed an infiltrating ductal carcinoma, grade II, estrogen and progesterone receptor positive, but negative for HER-2/neu protein (ER positive; PR positive; HER-2/neu negative). The proliferation fraction measured by Ki-67 was 40%. The morphologic and immunohistochemical patterns were consistent with a diagnosis of a primary in the breast (**Table 1**). Staging CT scan revealed a metastatic lesion in liver and bilateral pulmonary metastases. An attempt at guided biopsy from the pulmonary lesion was unsuccessful and led to pneumothorax. The patient refused further attempt at biopsy and agreed to be treated with Letrozole, considering that the pattern of metastases was more likely secondary to breast cancer rather than the ovarian cancer. Ten months

***Corresponding Author:** Ikram Burney, Senior Consultant, Medicine, Oman.
Email: ikram@squ.edu.om
Received: Dec 09, 2021 Accepted: Dec 25, 2021 Published: Jan 03, 2022

**Citation:** Ikram Burney. Hereditary breast ovarian cancer syndrome: One case, multiple lessons. IJ Clin Img and med Rew. 2022; 1(1): 1010.

later, the CT scan showed a marked regression in the size of pulmonary lesions, but a stable liver lesion (**Figure 2**).

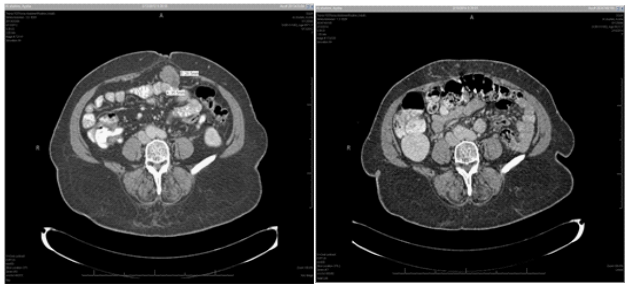

Fig 1A Fig 1B

**Figure 1:** CT scan at the time of the 3rd relapse (Figure 1A) shows a 35 mm x 28 mm mass in the region of omentum, which disappeared completely after 6 cycles of carboplatin AUC 4 (Figure 1B).

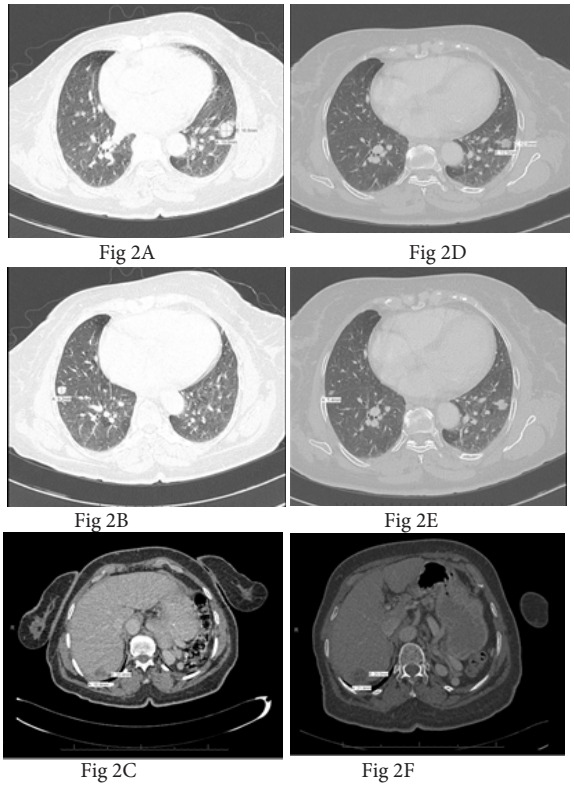

Fig 2A Fig 2D

Fig 2B Fig 2E

Fig 2C Fig 2F

**Figure 2:** Staging CT scan at the time of the diagnosis of breast cancer. Figures 1A, B and C metastatic lesions in left middle zone of lung, right middle zone of lung and the liver respectively, which regressed after 10 months of treatment with letrozole, as shown in figures 1D, E and F in the corresponding areas.

Considering that the patient had HBOCS, the patient was referred to the cancer geneticist. A detailed history revealed that her mother had dies of a malignancy of unknown primary site, her sister died at the age of 40 years, of a malignancy with ascites, but the primary site was not known to the patient or the family. The patient underwent counseling followed by assessment with a germline mutational analysis for breast and ovarian cancer panel, which revealed a pathogenic mutation in BRCA2 gene (c.4243G>T), and a variant of unknown significance in the NBN gene (c.425A>G). The BRCA2 mutation was consistent with a diagnosis of HBOCS. One year later, the CA 125 was seen to rise again serially, while the metastatic lesions in the lung and liver were under good remission. The patient was commenced on treatment with Olaparib, and the CA 125 dropped from 324 to 26 in one year (figure 3). The patient continued to receive Letrozole. Twelve years after the diagnosis of ovarian cancer, and while still on treatment for breast and ovarian cancer, the patient passed away of an unrelated cause. During the course of the treatment, patient's three daughters agreed for mutational analysis; two tested positive for mutation on the BRCA2 gene, and one of those two was screen-detected to have a breast cancer.

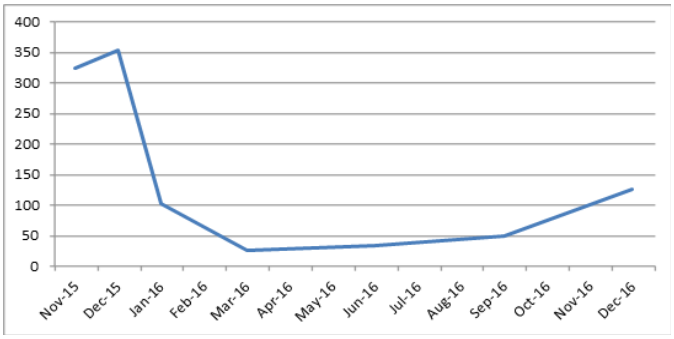


**Figure 3:** Serum CA 125 levels (IU/L) plotted over time. The patient was commenced on treatment with olaparib in Nov 2015. The levels dropped to within the normal limits (<36IU/L) in March 2016 (within 4 months of the treatment).

## Discussion

We report the case of a woman diagnosed to have HBOCS, who lived 12 years after the diagnosis of high grade ovarian cancer, received multiple lines of intra-venous chemotherapy, albeit with difficulty, underwent a secondary cyto-reductive surgery, and in the last 4 years of her illness was treated for the two cancers with an oral aromatase inhibitor and a PARP inhibitor. Both breast and ovarian cancers responded to the treatment with the two oral agents. We would like to highlight several aspects of management for the general readership of this journal.

The median survival of patients diagnosed to have high grade ovarian cancer, stage IIIC is dismal at around 3-4 years [8]. This patient lived for 12 years. Complete response to chemotherapy on five occasions, and a poor tolerance to chemotherapy, even at an age of 57-65 years indicate the tumor is exquisitely sensitive, especially to platinum containing chemotherapy. Platinum derivatives (Cisplatin, Carboplatin and Oxaliplatin) are alkylating agents, which act by disrupting the DNA repair pathways. Usually, PARP (Poly (ADP-ribose) polymerase) enzyme is required for base excision repair (BER). If the enzyme were inhibited, DNA repair would be affected. Also, if one allele is inactivated on the BRCA 1 or 2 gene, such as, because of mutations or methylation, DNA repair will be grossly affected, leading to a process called 'synthetic lethality' [9, 10]. In the last few years, three such compounds (Olaparib, Niraparib and Rucaparib) have been developed, tested, and have become the standard of care for patients with either germline BRCA mutations, or even in patients who may have homologous reconstitution deficiency [11, 12, 13, 14]. The first-in-class compound was Olaparib, approved by the FDA in 2014 for use as a single agent in patients who had germline BRCA mutations and had failed three lines of chemotherapy [15]. Our patient was treated and responded to the treatment.

BRCA 1 mutation is more common than mutation in BRCA 2 gene, and it is important to distinguish between the two. Although, response to platinum chemotherapy or PARP inhibitors is the same [10]. there are phenotypic differences, especially for breast cancer, and the sus-

ceptibility to develop other cancers, required for counseling the family members. Patients with BRCA 1 mutation are associated with triple-negative breast cancer (ER negative; PR negative; HER-2/neu negative) in more than 75% of the cases, whereas, patients with BRCA 2 mutations are associated with hormone-receptor positive breast cancer in more than two thirds of the cases [17]. Our patient had BRCA 2 mutation and hormone-receptor positive breast cancer, which was treated with aromatase inhibitor for more than 4 years. Although the life-time risk of developing breast cancer is same (65-70%) in the patients and the first-degree relatives, the life-time risk of ovarian cancer is 40-45% in case of BRCA 1 mutation carrier and 10-15% in case of BRCA 2 mutation career [16, 17]. Our patient had three daughters and they were counseled. Two tested positive for the same mutation. Because of their relatively young age, and the minimal increased risk of ovarian cancer in BRCA 2 mutation carriers, till the age of 45 years, they were advised to consider delaying BSO.

The role of secondary cyto-reductive surgery in ovarian cancer has been contemplated and debated over the last several years. Three major phase III trials have been reported in the past 2 years (Please see table 2). The GOG-0213 trial was the first trial to have been reported [18]. The primary end point was overall survival (OS); 485 patients were randomized to receive standard of care chemotherapy with or without secondary cyto-reductive surgery. The patients were selected if the treatment free interval from the last dose of platinum containing chemotherapy was more than 6 months. Although, there was a non-significant prolongation in the progression-free survival (PFS) (18.9 vs 16.2 month; HR 0.82), there was no difference in OS. Actually, the OS was inferior in the group which received secondary cyto-reductive surgery (50.6 vs 64.7 months; HR 1.29). However, a sub-set of patients who achieved R0 resection had a better PFS and OS, compared to those who could not have a R0 resection. The DESKTOP III trial randomized 407 patients to receive standard of care chemotherapy with or without secondary cyto-reductive surgery [19]. There was a clinically and statistically significant prolongation in the PFS (19.6 vs 14 months; HR 0.66). Also, the primary end-point was met [22]. The was a significant 7.6 months prolongation in OS (53.6 vs 46 months; 0.75 (0.58-0.96; P = 0.02). In addition to the criteria of treatment free interval of more than 6 months, the investigators also used the AGO criteria. The AGO criteria was developed after the DESKTOP I trial, and women with no gross residual disease after primary surgery, ECOG performance status of <1, and no ascites on CT scan at recurrence were classified as AGO score positive [20]. Subsequently, the DESKTOP II trial suggested that patients with a good performance status, absence of ascites at the time for secondary cyto-reductive surgery, more than 12 months of platinum-free interval, isolated site of recurrence, and the possibility of complete resection of disease were likely to benefit from the secondary cyto-reductive surgery [21]. The 3rd trial (SOC-1 trial) randomly assigned 356 patients with recurrent ovarian cancer in first relapse to either chemotherapy, or cyto-reductive surgery and chemotherapy [23]. There was a clinically meaningful (5.5 months), and statistically significant prolongation in the PFS (17.4 vs 11.9 months; HR 0.58) for the combination of cyto-reductive surgery and chemotherapy arm. The eligibility criterion was different from the first two studies. The SOC1 investigators selected patients if the platinum-free interval was at least 6 months, and an integrative model score was <4.7. However, at the time of management of our patient, results of the randomized trials were not available. We based our decision on the available data from DESKTOP I and II trials. The patient fit both the AGO score positive and the subsequent criterion developed after DESKTOP II trial. Our patient lived more than 5 years after the cyto-reductive surgery without a subsequent recurrence in the abdominal cavity.

Taken together, the three randomized trials comparing chemotherapy with or without cyto-reductive surgery suggest that there may be a benefit for surgery in carefully selected patients who can undergo potentially complete (RO) resection in women who have recurrent platinum-sensitive ovarian cancer. Although, results of randomized trials should not be compared, however, it would be useful to note that the magnitude of benefit seen in the DESKTOP III trial (HR 0.75), is similar to the recently reported SOLO2 study. The later study compared the OS in patients with platinum-sensitive ovarian cancer, but who also had a BRCA mutation, and who were treated with the PARP inhibitor, olaparib and had a median OS of 51.7 months compared to 38.8 months in the placebo arm with a HR of 0.74 [24]. Although, olparaib is the standard of care for maintenance treatment in patients with BRCA mutated platinum-sensitive ovarian cancer, the cost of drug and the overall cost of management remains very high. Cyto-reductive surgery in carefully selected patients, with a potential to achieve R0 resection may be an alternative, especially for patients with BRCA negative platinum sensitive ovarian cancer in first relapse.

In conclusion, we report the case of a patient with HBOCS, and highlight the recent developments in the systemic and surgical management of patients with ovarian cancer.

## Conflict of Address

### Ikram Burney:

Principal Investigator for the hospital site for Astra-Zeneca sponsored PREDICT study Served on the advisory board for Astra Zeneca Other authors declare no conflict of interest.

### Author's contribution:

Dr Juhaina Al Hinai – Data curation; Writing – original draft.

Dr Moza Al Kalbani – Surgical Oncology management, Methodology; Writing – review & editing.

Dr Marwa Al Riyami – Pathology reporting, methodology; Writing – review & editing.

Dr Abeer Al Sayegh – Clinical Genetics management, methodology; Writing – review & editing.

Dr Ikram A Bunrey - Conceptualization; Formal analysis; Supervision; Writing – original draft; Writing – review & editing.

### Informed Consent:

All data are anonymised, and patient identification is not possible.

## References


1. Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A., Jemal, A., 2018. Global cancer statistics. GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424. https://doi.org/10.3322/caac.21492.

2. Kurman R.J., Carcangiu M.L., Herrington C.S., Young R.H.WHO Classification of Tumours of Female Reproductive Organs.4th ed. WHO; Geneva, Switzerland: 2014.

3. Zhang S, Royer R, Li S, et al. Frequencies of BRCA1 and BRCA2 mutations among 1,342 unselected patients with invasive ovarian cancer. Gynecol Oncol. 2011;121:353-357.

4. Mikki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman S, et al. A strong candidate for the breast and ovarian cancer susceptibility gene BRCA1. Science. 1994;266:66-71.

5. Claus EB, Schildkraut JM, Thompson WD, Risch NJ. The genetic attributable risk of breast and ovarian cancer. Cancer. 1996;77:2318-2324.

6. Easton DF, Bishop DT, Ford D, Crockford GP. The Breast Cancer Linkage Consortium. Genetic linkage analysis in familial breast and ovarian cancer: results from 214 families. Am J Hum Genet 1993;52:678-701.

7. Easton DF, Steele L, Fields P, Ormiston W, Averill D, Daly PA, et al. Cancer risks in two large breast cancer families linked to BRCA2 on chromosome 13q12–13. Am J Hum Genet. 1997;61:120-128.

8. Peres LC, Cushing-Haugen KL, Kobel M, et al. Invasive epithelial ovarian cancer survival by histotype and disease stage. J Natl Cancer Inst. 2019;111:60-68.

9. Helleday T. the underlying mechanism for the PARP and BRCA synthetic lethality: clearing up the misunderstandings. Mol Oncol. 2011;5(4):387-393.

10. Konstantinopoulos PA, Spentzos D, Karlan BY, et al. Gene expression profile of BRCAness that correlates with responsiveness to chemotherapy and with outcome in patients with epithelial ovarian cancer. J Clin Oncol. 2010;28:3555-3561.

11. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. Lancet Oncol. 2014;15:852–861.

12. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med. 2016;375:2154-2164.

13. Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2017;18: 274-1284.

14. Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;390:1949-1961.

15. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012;366:1382-1392.

16. Antoniou A, Pharoah PD, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 2003;72:1117-30.

17. Hartmann LC and Lindor NM. The role of risk-reducing surgery in hereditary breast and ovarian cancer. N Eng J Med. 2016;374:454-468.

18. Coleman RL, Spirtos Nm, Enserro D, Herzog TJ, Sabbatini P, Amstrong DK et al. Secondary surgical cytoreduction for recurrent ovarian Cancer. N Eng J Med. 2019;381:1929-1939. [DOI: 10.1056/NEJMoa1902626].

19. Du Bois A, Vergote I, Ferron G, Reuss A, Meier W, Greggi S, et al. Randomized controlled phase III study evaluating the impact of secondary cytoreductive surgery in recurrent ovarian cancer: AGO DESKTOP III/ENGOT ov20. J Clin Oncol. 2017;35:15-5501. [DOI: 10.1200/JCO.2017.35.15_suppl.5501].

20. Harter P, Du Bois A, Hahmann M, Hasenburg A, Burges A, Lobi S, et al. Surgery in recurrent ovarian cancer: the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) DESKTOP OVAR trial. Ann Surg Oncol. 2006;13(12):1702-10.

21. Harter P, Sehouli J, Reuss A, Hasenburg A, Scambia G, Cibula D, et al. Prospective validation study of a predictive score for operability of recurrent ovarian cancer: the multicenter intergroup study DESKTOP II. A project of the AGO Komission OVAR, AGO, study group, NOGGO, AGO-Austria, and MITO. Int J Gynecol Cancer. 2011;21(2):289-95

22. Du Bois A, Sehouli J, Vergote I, et al. Randomized phase III study to evaluate the impact of secondary cytoreductive surgery in recurrent ovarian cancer: final analysis of DESKTOP III/ENGOT-ov20. J Clin Oncol. 2020; 38:15 (abs 6000). https://doi.org/10.1200/JCO.2020.38.15_suppl.6000

23. Zang R, Zhu J, Shi T, et al. A randomized phase III trial of secondary cytoreductive surgery in later recurrent ovarian cancer: SOC1:SGOG-OV2. J Clin Oncol. 2020;38:15 (abs 6001). [DOI: 10.1200/JCO.2020.38.15_suppl.6001].

24. Poveda A, Floquet A, Ledermann JA. Final overall survival (OS) results from SOLO2/ENGOT-ov21: A phase III trial assessing maintenance olaparib in patients (pts) with platinum-sensitive, relapsed ovarian cancer and a BRCA mutation. J Clin Oncol. 2020;38:15 (abs 6002) [DOI: 10.1200/JCO.2020.38.15_suppl.6002].