CASE REPORT

Response to Carboplatin and Paclitaxel in the treatment of hereditary breast ovarian cancer syndrome (HBOC): a case report

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Abstract

The co-occurrence of primary breast cancer and primary ovarian cancer is an exceptional hereditary phenomenon and results from inherent mutations in critical genes like BRCA1/2, PALB2, TP53, CHEK1, and ATM. We present here a unique case of hereditary breast-ovarian cancer syndrome (HBOC) reported in Combined Military Hospital, Lahore, Pakistan. It was marked by pathogenic variants in RAD51D, PALB2, CHEK1, and TP53 genes. Remarkably, the patient exhibited an outstanding response to the chemotherapy agents, Carboplatin and Paclitaxel. This dynamic treatment not only led to nearly complete remission of high-grade ovarian serous cancer but also triggered regression in grade-2 invasive ductal breast cancer after just a few rounds of chemotherapy. Consequently, what started as palliative care evolved into a curative triumph.

Keywords: Hereditary breast ovarian cancer, Breast cancer, Ovarian cancer, HBOC, BRCA, PALB2, Chemotherapy, Carboplatin, Paclitaxel.

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Introduction

Worldwide, the occurrence of cancer is on a rising trajectory. Notably, breast cancer stands out as the predominant form of cancer affecting women across the world. In Pakistan, one out of every nine women is affected by breast cancer, constituting 46.3% of all cancer cases. Alarmingly, Pakistan exhibits the highest prevalence of breast cancer in South Asia, with an Age Standardised Rate (ASR) of 69.1 per 100,000 individuals. In contrast, ovarian cancer ranks as the sixth most prevalent type of cancer, contributing to 6.6% of all cancer diagnoses.[1,2]The concurrent presence of these two tumours as primary tumours in hereditary breast ovarian cancer (HBOC) syndrome represents an exceedingly uncommon hereditary condition stemming from germ-line mutations in predisposed genes. HBOC is responsible for 5-10% of breast cancers. Individuals affected by this disorder exhibit a heightened predisposition to the development of breast and ovarian cancers compared to the general population. Beyond its association with breast and ovarian malignancies, HBOC extends its influence to various other cancer types, including pancreatic cancer, prostate cancer, and melanoma.[3]

Prompt detection of the ailment and identification of the culpable pathogenic variant are paramount for achieving remission in both the cancers, necessitating careful selection of the most effective chemotherapy regimen.

This report illuminates one such distinctive case of familial primary ovarian high-grade serous carcinoma concomitant with triple-negative grade-2 primary invasive ductal breast carcinoma. Moreover, the case also exhibited a marked positive response to the chemotherapeutic agents, Carboplatin and Paclitaxel. This dynamic treatment not only led to nearly complete remission of high-grade ovarian serous cancer but also triggered regression in grade-2 invasive ductal breast cancer after just a few rounds of chemotherapy.

Case Report

This case report is based on an extraordinary case of a 42-year-old female who reported to the Combined Military Hospital, Lahore, Pakistan. She was diagnosed with familial primary ovarian serous carcinoma simultaneously with primary breast carcinoma. She had a strong family history of ovarian and breast cancers. Her mother was diagnosed with ovarian carcinoma whereas two of her sisters were diagnosed with breast cancer.

The patient presented with symptoms of abdominal distention, bloating, constipation, and anorexia for the first time in October 2022. Initially, she was conservatively treated. However, over the course of two weeks, abdominal distention progressively increased, and she experienced associated abdominal pain and exertional dyspnoea. Subsequently, she was admitted to CMH

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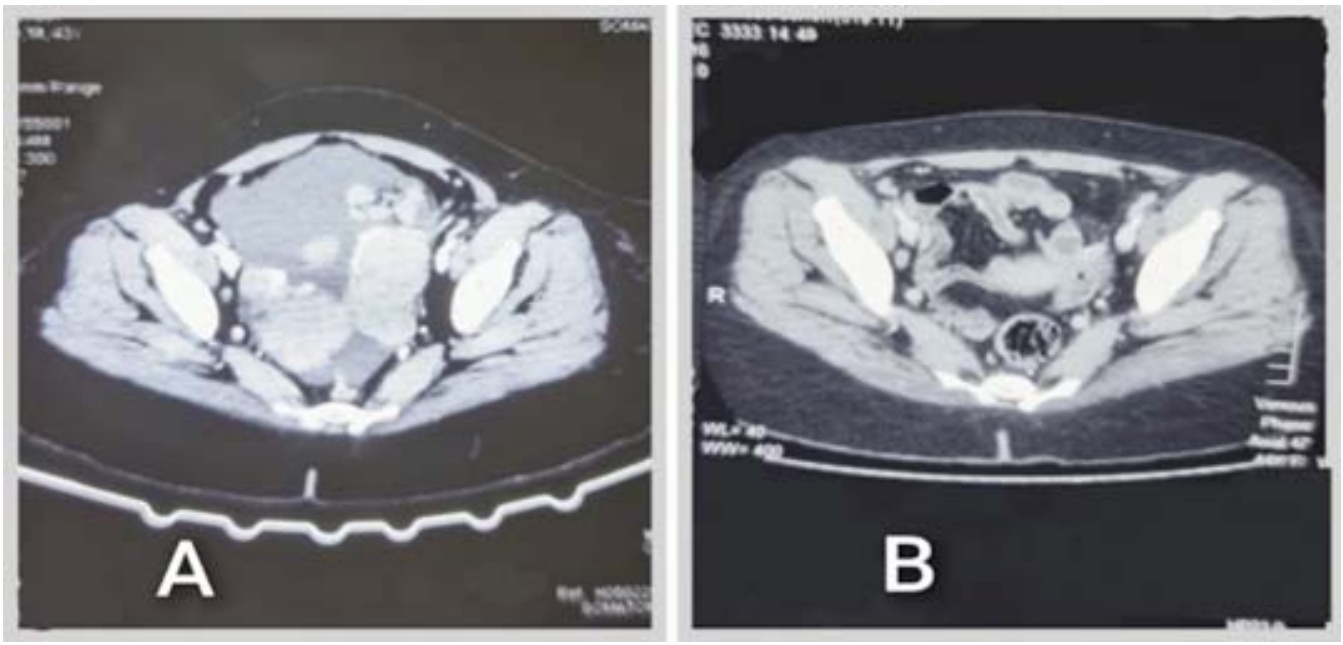

Figure-1: CT scan of the abdomen and pelvis showing bilateral adnexal mass. Before (A) chemotherapy and after (B) chemotherapy.

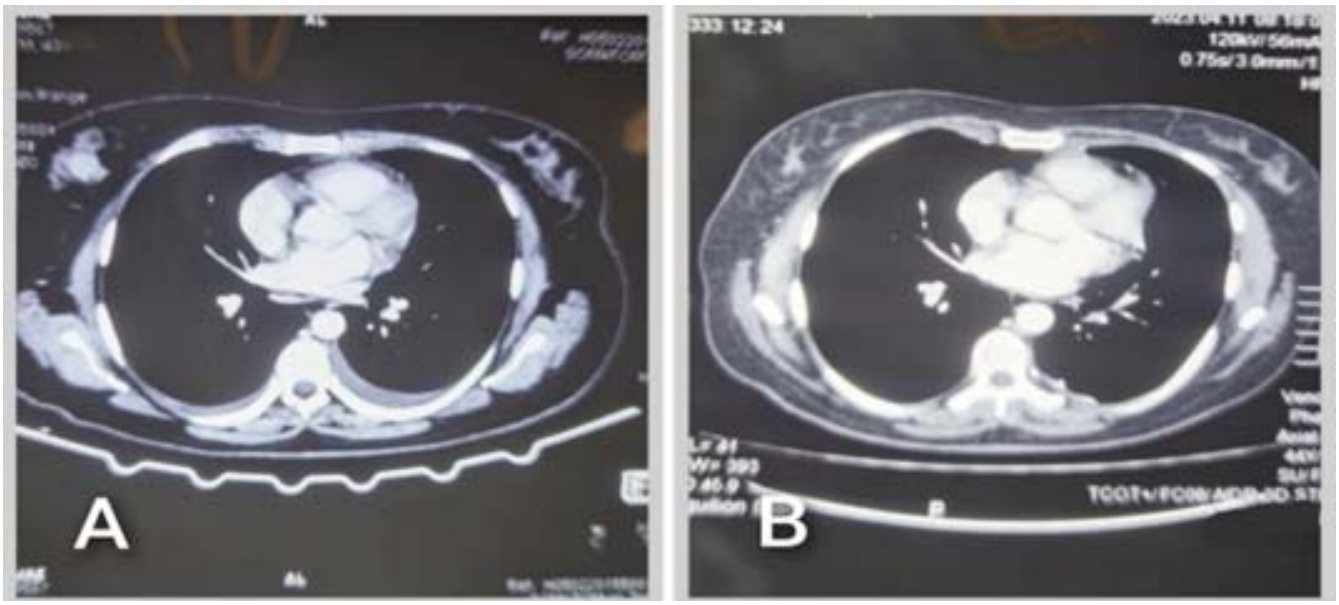

Figure-2: CT scan of the chest showing right breast mass. Before (A) and after (B) chemotherap.

Lahore. An abdominal ultrasound revealed bilateral solid adnexal masses, followed by a contrast-enhanced CT scan of the abdomen and pelvis, showing two large soft tissue attenuation mass lesions in bilateral adnexa measuring 5.5x5.9x4.8 cm in the right adnexa and 7.4x4.3x7.5 cm in the left adnexa. There was mild to moderate pleural effusion and abdominopelvic ascites. Additionally, an incidental soft tissue attenuation mass lesion was found in the right breast as shown in Figure 1 (A) and Figure 2 (A). Tumour marker CA-125 was sent in correlation with the above findings and returned positive (1259 U/ml). The patient underwent diagnostic and therapeutic ascitic tap for cytological examination, which was positive for cancer cells.

Considering all the above findings, a biopsy of the adnexal mass was taken, which showed high-grade serous carcinoma positive for PAX8 and WT1 and negative for GATA3, with aberrant overexpression of P53. Furthermore, a tru-cut biopsy was taken of the right

breast mass, revealing invasive ductal breast carcinoma grade 2. Immunohistochemical studies revealed it to be a triple negative cancer showing negativity for oestrogen (ER), progesterone (PR), and HER2 receptors, and positivity for GATA3 and CK.

A next-generation sequencing (NGS) solid tumour panel somatic analysis was performed, and a pathogenic variant was identified in the RAD51D gene. Moreover, likely pathogenic variants were identified in the TP53, PALB2, RBM10, and CHEK1 genes. These variants are considered Tier2, based on known or predicted status as tumour driver mutations. Whereas, BRCA results were negative.

Subsequently, chemotherapy was started the following month. Carboplatin and Paclitaxel were introduced as the chemotherapeutic agents of choice for ovarian serous carcinoma. These agents also targetted and covered familial invasive ductal breast carcinoma. The patient received 18 cycles of chemotherapy, done on a weekly basis. Astonishingly, the ovarian serous carcinoma showed marked sensitivity to Carboplatin and Paclitaxel, and mid-cycle assessment revealed complete remission of ovarian serous cancer and regression of invasive ductal breast carcinoma grade 2 to local breast disease with level-1 axillary lymph nodes on CT scan. After the completion of 18 cycles of chemotherapy, remission was confirmed by normal serum CA-125 levels of 9.9 U/ml and a repeat contrast-enhanced CT chest abdomen pelvis scan which showed no evidence of adnexal mass and a regressed local breast nodule as shown in Figure 1(B) and Figure 2(B).

Surgical intervention, including risk-reducing Total Abdominal Hysterectomy Bilateral Salpingo-oophorectomy (TAHBSO), is planned for this patient. Moreover, profound sensitivity to Carboplatin and Paclitaxel with PALB2 and CHEK1 pathogenic variants, makes this patient a good candidate for PARP inhibitors as maintenance therapy after the surgical intervention.

The patient had her last follow-up a month ago, where CT scan showed no evidence of any recurrence or residual disease. Furthermore, CA-125 levels were also normal.

Consent was taken from the patient to publish her case.

Discussion

Breast cancer stands as a pervasive global malignancy, holding the title of the most widespread cancer among women internationally. Correspondingly, ovarian cancer secures its place as the sixth most prevalent cancer among women on a global scale and takes the lead as the most common gynaecological tumour among women in Pakistan.[4,5]

Generally, breast and ovarian cancers are sporadic in nature. Yet, their hereditary transmission is an infrequent occurrence and rarely are they passed from generation to generation contributing to a mere 10-15% of all diagnosed breast cancers.[6]

While there are multiple risk factors and aetiologies for non-familial cancers, hereditary (non-familial) breast and ovarian cancers are mainly caused by mutations in susceptible genes. Most hereditary breast and ovarian cancers are caused by mutations in the BRCA1 and BRCA2 genes, which encode tumour-suppressor proteins. PALB2 mutation is the second most common mutation after BRCA, with its mono-allelic phenotype involved in hereditary breast-ovarian cancer. In addition to BRCA and PALB2 genes, many other non-BRCA1/2 gene mutations are involved in hereditary breast-ovarian cancer, including ATM, BRIP1, CHEK2, RAD50, RAD51C, TP53, etc.[7,8]

Patients with HBOC mutations should undergo rigorous screening modalities for early diagnosis and treatment. For individuals with BRCA1/2 or PALB2 mutations, screening with Magnetic Resonance Imaging (MRI) should begin at the age of 30 years or five years before the age the last family member was affected by breast cancer. Surveillance for ovarian cancer primarily involves semi-annual transvaginal ultrasound assessments and tracking of CA-125 tumour marker levels.[9]

A spectrum of chemotherapy choices exists for ovarian serous carcinoma, ranging from platinum-based regimens to combined approaches involving Paclitaxel. In this case, an intriguing course of 18 cycles featuring a dynamic combination of Carboplatin and Paclitaxel was chosen. This choice stems from the proven advantages of combination therapy, offering superior progression-free survival outcomes and minimising adverse effects compared to the traditional single-agent Carboplatin/Paclitaxel chemotherapy.[10]

Furthermore, a pharmaceutical marvel known as Poly (ADP Ribose) Polymerase (PARP) inhibitors have demonstrated extraordinary efficacy as maintenance therapy for HBOC post-chemotherapy and risk-reducing surgeries. The magic lies in PARP inhibitors disrupting the DNA repair mechanism, causing double-stranded breaks in the DNA, ultimately triggering apoptosis—the cellular curtain call.[11] The current patient will also be started on PARP inhibitors as maintenance therapy after risk-reducing TAHBSO.

Fortunately, the rise of genetic testing over the past decade has resulted in better evaluation and

management of cancer patients, as it serves as a prognostic predictor and helps in choosing the most suitable chemotherapy regimen.

Conclusion

Combination Carboplatin-Paclitaxel chemotherapy has shown remarkable results in the treatment of HBOC harbouring PALB2, BRCA, RAD51D, and CHEK1 pathogenic variants. This treatment is followed by risk-reducing TAHBSO and maintenance therapy with PARP inhibitors.

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FM: Design, editing, reviewing, responsible for integrity and final approval.
MT: Design, drafting, editing and reviewing.
AA, IAR: Reviewing, revision and final approval.