Case Report

A Case of Triple-Negative Breast Cancer with Germline Pathogenic Variants in Both *BRCA1* and *BRCA2*

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Keywords

Triple-negative breast cancer · *BRCA1* · *BRCA2* · Recurrence

Abstract

We report a rare case of hereditary breast and ovarian cancer syndrome (HBOC) with pathogenic variants in both *BRCA1* and *BRCA2*. The patient was a 78-year-old woman who visited the hospital after noticing a lump in her left breast 6 months before, which gradually increased in size. According to her family history, her maternal aunt developed breast cancer in her 40s. On palpation, a 4-cm large mass was palpated in the upper outer part of the left breast. A needle biopsy revealed invasive ductal carcinoma of the breast, which was negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor type 2. The patient was diagnosed with cT2N0M0 stage IIA, and primary systemic treatment was planned. The patient developed drug-induced interstitial pneumonia after receiving paclitaxel. Although she recovered spontaneously, she did not wish to receive further chemotherapy, and thus surgery was performed. Four months after the surgery, the patient became aware of dyspnea. After a thorough examination, she was diagnosed with postoperative cancer recurrence of the left breast with multiple liver metastases, cancerous peritonitis, multiple bone metastases, and multiple lymph node metastases. Genetic testing was performed, and pathogenic variants were found in both *BRCA1* and *BRCA2*. However, her condition worsened, and she died 8 months after the surgery. *BRCA* pathogenic variants had more advanced breast cancer on initial diagnosis and worse cancer-related outcomes. It is desirable to consider the optimal approach to the treatment of breast cancer in pathogenic variants. In elderly patients with triple-negative breast cancer, HBOC may be suspected, based on biomarkers and family history. It is important to provide information on genetic counseling, genetic testing, and effective treatment plans proactively.

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Introduction

Hereditary breast and ovarian cancer syndrome (HBOC) is one of the most common hereditary tumors caused by germline pathogenic variants of *BRCA1* or *BRCA2* and results in a high risk of developing breast or ovarian cancer [1, 2]. In recent reports, *BRCA* pathogenic variants remained an independent poor prognostic factor for cancer recurrence or death [3]. Also, rare cases of pathogenic variants in both *BRCA1* and *BRCA2* have been reported quite exceptionally in non-Ashkenazi individuals [4–6]. In this study, we report a case of triple-negative breast cancer (TNBC) with both *BRCA1* and *BRCA2* pathogenic variants that were revealed after early recurrence.

Case Report/Case Presentation

The patient was a 78-year-old woman who visited the hospital after noticing a lump in her left breast 6 months before, which gradually increased in size. She had no previous medical history or comorbid diseases. She did not take any medications, nor had she been subject to any hazardous exposures. She had a positive familial history of breast cancer and other cancers (Fig. 1). In her family history, her maternal aunt (II-10) developed breast cancer in her 40s and died in her 50s. Also, her sister (III-11) developed esophageal cancer at the age of 58 and died at the age of 62. Another 68-year-old sister (III-13) developed gastric cancer in her 30s and bladder cancer in her 40s. And, her father (II-2) developed bladder cancer in his 70s and died at the age of 94. Three paternal uncles (II-4, II-5, and II-6) and another maternal aunt (II-12), whose details are unknown, contracted cancer and died in their 70s.

Palpation revealed a 4-cm large, irregularly shaped, firm mass in the upper lateral region of her left breast. A mammography identified a high-density mass with finely serrated margins in the middle-outer region of the left breast (Fig. 2a, b). A breast ultrasound revealed a 25 × 31 × 24 mm segmental, well-defined, coarse, hypoechoic mass in the left 1:00 central portion (Fig. 2c). The breast MRI showed a 39 × 30 × 25 mm mass in the upper lateral portion of the

Fig. 1. Family tree of the patient: proband of this case; III-10, maternal aunt; II-10 developed breast cancer in her 40s and died in her 50s.

Fig. 2. **a, b** Mammogram; marginal micrographs in the middle-outer region of the left breast: a serrated hyperintense mass was found. **c** Breast ultrasound before PST: a hypoechoic mass of $25 \times 31 \times 24$ mm was found (left) at 1 o'clock at the central portion. **d** Breast MRI before PST; $39 \times 30 \times 25$ mm mass was found in the left upper lateral breast. **e** CT; diffuse reticular shadows in all lung fields were identified and determined as drug-induced interstitial pneumonia. **f** CT taken to assess pneumonia showed no apparent liver metastasis. **g** Breast MRI after PST; mass reduced to $16 \times 13 \times 18$ mm. CT, computed tomography; PST, primary systemic treatment.

left breast, with early dark staining and a prolonged contrast effect (Fig. 2d). A needle biopsy was performed on the mass, which diagnosed invasive ductal carcinoma of the breast; Ki-67 labeling index: 60%; histological grade: grade II; immunohistological evaluation showing TNBC that lacked expression of estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor type 2 (HER2); and clinical stage IIA.

The patient was scheduled for primary systemic treatment (PST) and 12 cycles of weekly paclitaxel followed by 4 cycles of EC therapy. After 11 cycles of paclitaxel, the patient developed drug-induced interstitial pneumonia (Fig. 2e). The respiratory physician was consulted. As the clinical symptoms were mild, outpatient follow-up was decided on. The symptoms resolved spontaneously within approximately 2 weeks. Also, CT at the onset of pneumonia did not detect apparent metastasis including the liver (Fig. 2f). Adverse events, such as peripheral neuropathy and malaise, were moderate. The patient did not wish to receive further chemotherapy.

The reduction rate of the mass was 55%, and the treatment effect of PST was determined as a partial response (Fig. 2g). Surgery consisted of a total left mastectomy and sentinel lymph node biopsy. The histopathological examination revealed the following: invasive ductal carcinoma, scirrhous type, tumor size $2.0 \times 0.9 \times 1.5$ cm, no vascular invasion, negative margins, Ki-67 labeling index: 32%, histological grade: grade II, preoperative histological grade: grade II, preoperative response to drug therapy: grade 1a, 1-mm micrometastasis in the sentinel lymph node, and pathological stage IB. An immunohistological evaluation showed TNBC that lacked ER, PgR, and HER2 expressions. The patient did not wish to receive additional postoperative drug therapy and was placed on a follow-up treatment plan. Four months after the surgery, the patient began to experience dyspnea, which worsened gradually. Based on a thorough examination, we diagnosed postoperative cancer recurrence of the left breast with multiple liver metastases, cancerous peritonitis, multiple bone metastases, and multiple lymph node metastases (Fig. 3a–h).

Fig. 3. CT: **a** multiple liver metastases occupying the entire liver. **b** Pleural effusion on the left side superiority was recognized. PET: **c–h** FDG accumulation to the bone of the whole body such as the vertebral body and pelvis, left clavicle upper cavity lymph node, para-aortic lymph node, and strong FDG accumulation to the liver were recognized. These result in multiple bones, lymph nodes, liver metastasis, and carcinomatous pleurisy. CT, computed tomography; PET, positron emission tomography; FDG, ^{18}F -fluorodeoxyglucose.

Genetic testing was performed as a companion diagnosis, and pathogenic variants were found in both *BRCA1* and *BRCA2*, c.5278-1G>A and c.6925C>T (p.Arg2318*), respectively. The history of breast cancer of the maternal aunt (Fig. 1, indicated by II-10) was clear, and it was considered that the germline pathogenic variant of *BRCA* might be from the maternal direction. After receiving these results, her husband and eldest son (Fig. 1, indicated by IV-1) were referred to genetic counseling. They did not wish to explain the results to account for the mental and physical burden of the patient. The eldest son and the second son (Fig. 1, indicated by IV-2) want to take the examination, but are considering the timing of the examination. To date, no other family member, including her sister (Fig. 1, indicated by III-12) has received genetic testing. However, the patient's general condition continued to worsen and with no indication for drug therapy. The best supportive care was decided as the course of management. The patient was treated with palliative care and died 8 months after the surgery.

Discussion/Conclusion

HBOC is a susceptibility syndrome for breast and ovarian cancers caused by the pathogenic variant in the germline of either *BRCA1* or *BRCA2*; it is an autosomal dominant form of inheritance [1, 2]. The cumulative risk is reported as 72% for *BRCA1* and 69% for *BRCA2* in breast cancer by the age of 80 and 44% for *BRCA1* and 17% for *BRCA2* in ovarian cancer [7]. The frequency of HBOC in the general population is estimated to be 1 in 400 or 1 in 500, which

is extremely high for a hereditary disease [8]. In contrast, 3–5% of breast cancer patients and about 10% of ovarian cancer patients are said to have HBOC [9].

To date, the co-existence in an individual of the pathogenic variant in both *BRCA1* and *BRCA2* is a very rare condition in most populations, particularly in non-Ashkenazi Jewish [4–6], and our patient has no known Ashkenazi heritage. The frequency of them is estimated at 1.8% in Ashkenazi Jewish due to founder mutations, whereas in non-Ashkenazi Jewish, it is in the range of 0.2–0.8% [10] and 0.3% [11]. Also, the Japanese Organization for Hereditary Breast and Ovarian Cancer (JOHBOC) reported the number of *BRCA* tests and the results carried out in Japan in 2018. In that report, 3,477 cases were tested, and 6 cases (0.2%) had both pathogenic variants [12].

Wang et al. [3] implied the more aggressive nature of breast tumors in *BRCA* germline pathogenic variants. They showed that *BRCA* pathogenic variants were more likely to be diagnosed with breast cancer already spread to the regional lymph node, and their breast cancer-related outcomes were significantly worse. The 5-year disease-free survival rate was only 73.3% for pathogenic variants, in contrast to 91.1% for nonpathogenic variants. The *BRCA* pathogenic variants were an independent prognostic factor with an adjusted hazard ratio of 3.03 (95% CI: 1.40–6.58) for cancer recurrence death. The poor clinical outcome in pathogenic variants mainly resulted from recurrence as distant metastasis, therefore excluding the contribution by new primary cancer in the ipsilateral or contralateral breast, of which the risk had been known to be elevated in pathogenic variants.

In addition to pathogenic variants, this case involved micrometastasis in the axillary lymph nodes and non-pCR. She was at a high risk for recurrence. If the patient did not wish to receive postoperative treatment, it was important to be flexible by considering the individual patient's situation, such as by shortening the interval between regular visits to detect signs of recurrence.

As the clinical course of this case, the postoperative early recurrence was caused, and the prognosis was poor. It may raise up the possibility of a pejorative impact of either involved pathogenic variants or resulting from their association. Nevertheless, a review of the literature suggests that the co-existence of *BRCA1* and *BRCA2* pathogenic variants likely does not cause more severe phenotype of breast cancer with respect to age of disease onset, cumulative lifetime risk, and multiple primary tumors when compared with available population-specific cancer risk in carriers of a single *BRCA* pathogenic variant [4, 5]. It is an analysis of a small number of cases, and the evaluation of the prognosis is controversial. Further analysis by prospective accumulation is expected.

Both pathogenic variant-related breast cancers are usually of high grade. However, while there are no known histopathological features that distinguish *BRCA2* from sporadic tumors, breast cancers occurring in the *BRCA1* pathogenic variant are usually negative for expression of ER, PgR, and HER2 (the so-called triple-negative phenotype) and positive for p53 alterations [13]. According to a recent report, the breast cancers that occurred in the pathogenic variants were all high grade, stage II, mostly negative for hormonal receptors and/or HER2 expression, and with high proliferative index [14]. These data indicate that breast cancers in pathogenic variants are more likely to exhibit a *BRCA1* histopathological phenotype and suggest that in these patients, breast carcinogenesis is mainly driven by the pathogenic variant in *BRCA1*, even if this hypothesis requires confirmatory studies on a larger number of cases.

The increased risk of cancer in both pathogenic variants, as in patients with a single variant in *BRCA*, is not limited to breast and ovarian cancer but also involves other cancers [14]. In line with this evidence, among the tumors reported in the analyzed pathogenic variants' families, the most frequent was ovarian cancer (21.4%), followed by breast cancer, prostate cancer, and colon cancer, with a percentage of 14.3%, and bilateral breast cancer, breast and ovarian cancer, bladder cancer, leukemia, and laryngeal cancer, with a percentage of 7.1% [11].

We encountered a case of TNBC with pathogenic variants of *BRCA1* and *BRCA2* that caused early recurrence. *BRCA* pathogenic variants had more advanced breast cancer on initial diagnosis and worse cancer-related outcomes. Optimal approach to breast cancer treatment for pathogenic variants warrants further investigation. It is important that we strive to provide appropriate genetic counseling to patients and their families, in accordance with the NCCN guidelines [15]. Even in elderly TNBC patients, if HBOC is suspected, it is important to perform proactive genetic testing more and provide effective treatment.

Statement of Ethics

It was not necessary to obtain ethical approval for this case report. Written informed consent was obtained from the patient's family for the publication of this case report and the accompanying images.

Conflict of Interest Statement

All authors have no conflicts of interest to declare.

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Author Contributions

M.K. and Y.H. conceived and designed this study. All authors contributed to the data acquisition and analysis. M.K. and Y.H. were the major contributors in the writing of this manuscript. All authors have read and approved of the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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