A case of BRCA2-pathogenic variant breast cancer with metachronous endometrial cancer and pancreatic cancer: Case report and review of literature

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Case Report

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Abstract

Background: Since the popularization of cancer screening and an improvement in treatment over the last two decades, multiple primary malignant neoplasms (MPMNs) have been increasingly reported. We report a patient who developed metachronous multiple primary malignant neoplasms in the breast, the endometrium, and the pancreas over a period of 13 years.

Case presentation: A 42-year-old woman was first diagnosed with breast cancer and underwent breast-conserving surgery with adjuvant radiation therapy and endocrine therapy. Four years after breast surgery, she was diagnosed with endometrial cancer and underwent a laparoscopic modified radical hysterectomy with bilateral oophorectomy with pelvic lymph node dissection followed by adjuvant chemotherapy. However, there was peritoneal dissemination of endometrial cancer one year after surgery which could be removed laparoscopically followed by adjuvant chemotherapy. Ten years after breast cancer surgery, Pleural metastasis of breast cancer was diagnosed and treated by endocrine therapy. Thirteen years after breast cancer surgery, a pancreatic tumor with multiple liver masses emerged. It was difficult to diagnose whether primary or metastasis cancer by the results of the pathological analysis. Finally, we diagnosed primary pancreatic cancer with liver metastasis by clinical examination with the BRCA2-pathogenic variant. These tumors were well responded to chemotherapy and the patient survived during a follow-up period of 8 months.

Conclusions: According to MPMNs, breast cancer patients should be followed-up carefully for the possibility of BRCA pathogenic variant and development of different primary malignant neoplasms.

Background

Due to the prolonged survival of cancer patients, the diagnosis of multiple primary malignant neoplasms (MPMNs) has gradually increased with the incidence of 0.73–11.7% (1, 2) among cancer patients. Here, we report a case of a patient presenting with metachronous MPMNs of the breast, endometrium, and pancreas with a BRCA2 pathogenic variant.

Case Presentation

A case of a 42-year-old woman with hypothyroidism as comorbidity. The family history revealed that her mother had lung cancer, her paternal aunt had breast cancer, her paternal uncle had pancreatic cancer, and her maternal uncle had prostate cancer and malignant lymphoma. She presented with a left breast mass with pain. A core needle biopsy of breast mass showed ductal carcinoma in situ (DCIS). After several examinations, such as CT and MRI, she was diagnosed with breast cancer (cTisN0M0) and underwent breast-conserving surgery with sentinel lymph node biopsy. Pathological analysis showed grade 1 invasive ductal carcinoma (IDC) (T1N0M0, pStage I) (Fig. 1A) with estrogen receptor (ER)-positive, progesterone receptor (PR)-positive, and human epidermal growth factor receptor 2 (HER2)-negative. She received adjuvant radiotherapy (50Gy) and endocrine therapy (tamoxifen). At the age of 45
years, the follow-up CT scan revealed a tumor in the uterus (Fig. 2A). She was diagnosed with endometrial cancer and underwent a laparoscopic modified radical hysterectomy with bilateral oophorectomy with pelvic lymph node dissection. Pathological analysis showed localized endometrioid adenocarcinoma, exophytic type, ly0, v0, margin (-), grade 1 (pT1aN0M0) (Fig. 1B). Then she received 6 cycles of adjuvant chemotherapy, combined with paclitaxel and carboplatin. 1 year after, the follow-up CT scan revealed multiple intra-abdominal masses (Fig. 2B). As peritoneal dissemination from breast or endometrial cancer was suspected, laparoscopic peritoneal dissemination resection was performed. Pathological analysis of peritoneal tumor confirmed the dissemination of endometrioid adenocarcinoma (Fig. 1C). After 10 years after breast cancer surgery, mass lesions were noticed in her thoracic cavity on a follow-up CT scan (Fig. 3A). PET-CT scan showed an accumulation of SUV max = 2.5 (Fig. 3B). Video-assisted thoracoscopic surgery was performed to identify the primary lesion of this tumor. The pathological analysis revealed the tumor positive for ER, PgR and GATA-3, which led to the diagnosis of metastasis from breast cancer (Fig. 3C).

The patient then received an aromatase inhibitor after the surgery. Three years later, a pancreatic and hepatic mass was noticed (Fig. 4A and 4B). Although tumor markers of pancreatic cancer (DUPAN-2 and SPAN-1, CA19-9) were highly elevated, the other tumor markers (CEA, CA15-3) were slightly elevated (DUPAN-2 530 U/mL, SPAN-1 490 U/mL, CA19-9 2,492 U/mL, CEA 16.6 ng/mL, and CA15-3 30.3 U/mL). EUS-FNA was then performed and revealed adenocarcinoma with ER-negative, PgR-positive (partially), GATA-3-positive, PAX8-negative, GCDFP15-negative (Fig. 5).

These results could not diagnose the pancreatic tumor as a metastatic tumor from breast cancer or primary pancreatic cancer. A BRCA gene analysis was performed to investigate the possibility of primary pancreatic cancer. The result showed the BRCA2 pathogenic variant. DUPAN-2, SPAN-1, and CA19-9 levels were rapidly elevated while CEA and CA15-3 were stable (DUPAN-2 1,200 U/mL, and SPAN-1 1,300 U/mL, CA19-9 6,640 U/mL, CEA 18.5 ng/mL, and CA15-3 30.3 U/mL) during for one month. Based on these results, we diagnosed primary pancreatic cancer with liver metastasis and started chemotherapy with gemcitabine and nab-paclitaxel as pancreatic cancer treatment. One month later tumor markers of a pancreatic cancer were markedly decreased (CA19-9 1,592 U/mL, DUPAN-2 1000 U/mL, and SPAN-1 350 U/mL) (Fig. 6), although CA15-3 level was no change (28.6 U/mL). The patient has received systemic chemotherapy and is alive at 8 months after diagnosis of pancreatic cancer.

**Discussion**

Since the diagnosis and therapeutic outcomes of malignant tumors have improved due to the advancement of medical technology in recent years, the development of multiple cancers has been attracting concern (3). Breast cancer is the most common cancer in women and has a good prognosis, which makes it more likely to develop the other concomitant cancers. Since MPMNs were reported by Billroth et al. in 1889, the phenomenon of MPMNs has been defined by several researchers (4). It was generally defined as the coexistence of at least two unrelated primary malignancies in a single patient. In
1932, Warren and Gates classified MPMNs as metachronous (interval of more than 6 months) and synchronous (interval of less than 6 months between primary malignancies) (5).

In this literature review, we collected thirty-seven reports of MPMNs cases with three or more primary cancers, which included breast cancer as one of the primary cancers, including our case. We excluded case reports with genetic syndromes associated with increased susceptibility to breast cancer, such as Li-Fraumeni syndrome, Lynch syndrome, Cowden syndrome, CDH1-associated breast cancer, Peutz-Jeghers syndrome, and PALB2-associated breast cancer etc). To our knowledge, this is the first time to report the incidence of a combination of primary breast cancer, endometrial cancer, and pancreatic primary cancer in the reports of MPMNs. 19 cases (51%) were metachronous, 15 cases (41%) were synchronous, and 3 cases (8%) were both metachronous and synchronous (Fig. 7A). Breast cancer was the initial diagnosis in 69% of cases (Fig. 7B). Primary cancers Configuring MPMNs comprised colorectal cancer (17%), lung cancer (14%), urinary cancer (13%), head and neck cancer (10%), and gynecological cancer (9%) (Fig. 7C). However, these results may not represent the entirety of MPMNs because the rare cases were only reported. Jerry et al. reported that other previously diagnosed primary malignancies before breast cancer comprised gynecological cancer (27%), malignant melanoma (25%), and gastrointestinal carcinoma (18%) (6). They also reported that 0.8% were patients with three or more multiple primary cancers that included breast cancer.

Warren and Gates proposed three criteria for the diagnosis of MPMNs including 1) each tumor must present a definite clinical and histological picture of malignancy; 2) each tumor must be histologically distinct; and 3) the probability that one was a metastatic lesion from the other must be excluded (5). In our case, the diagnosis of the pancreatic tumor was particularly problematic. Immunohistochemical analysis of the pancreatic biopsy showed that the neoplastic cells were positive for GATA-3 and PgR while ER, GCDFP-15, Pax8 were negative. GATA-3 is positive in 74–90% of breast cancer, 37% of pancreatic cancer, and 7% of endometrial cancer (7–9). ER was positive in primary breast tumor and negative in pancreatic tumor in our case. However, ER expression could alter in metastatic site from primary site (10–12), it could not exclude that pancreatic tumor was metastatic lesion from breast cancer on this basis alone. Therefore, to definitively differentiate between metastases from breast cancer and primary pancreatic cancer, we considered multidisciplinary aspects including the clinical features, tumor markers, and BRCA analysis in our case.

MPMNs could be caused by a variety of endogenous, exogenous, genetic, and therapeutic factors (13, 14). It is also possible that a common etiology may play a pivotal role in the development of different malignancies, in which the common early genetic events occur at different time points and exhibit a long latency period (15). Genome-wide association studies have identified 72 loci associated with breast cancer susceptibility, 17 of which are associated with MPMNs (16). Since our patient has a family history of several cancers, the possibility of the involvement of genetic factors was high. BRCA pathogenic variant in women confers a high risk for breast cancer and ovarian cancer. Both BRCA1 and BRCA2 are involved in pathways that are important for DNA damage recognition, double-strand break repair, checkpoint control, transcription regulation, and chromatin remodeling. These functions are essential for
all cell types. Mutation of these genes will lead to the initiation and proliferation of cancer cells (17). Within minutes of DNA damage, the BRCA1 gene product is recruited to the sites of double-strand DNA breaks and initiates repair by modifying the local chromatin structure, thereby allowing other DNA repair proteins access to the damaged site. The BRCA2 protein is part of the homologous recombination DNA repair complex. These complex repairs double-strand breaks by homologous recombination through interaction with RAD51, a key component of the double-strand break repair pathway. In the absence of BRCA2, critical events in the initiation of homologous recombination are impaired; repair and replication errors accrue with each cell cycle (18).

BRCA2 pathogenic variant has been reported to the association with a high risk of not only breast and ovarian cancer but also prostate and pancreatic cancer. For pancreatic cancer, most research showed an increased risk to develop pancreatic cancer in individuals with BRCA pathogenic variants or individuals at high risk of having a BRCA pathogenic variant. The relative risk of pancreatic cancer for germline BRCA2 and BRCA1 pathogenic variants was 3.5–10 and 2.26, respectively, and the cumulative incidence was 2%-7% and 1%-3% respectively (19).

Our case is consistent with the features of existing reports of luminal type breast cancer and pancreatic cancers occurring in women with BRCA2 pathogenic variants. As for endometrial cancer, Marthe M et al. pointed out the association between endometrial cancer and BRCA1/BRCA2 mutation. They studied 6,000 germlines BRCA1/2 mutation carriers and 8,451 non-BRCA1/2 mutation carriers and observed over 22 years and found a significant 2–3 fold increased risk of Endometrial cancer in BRCA1 or BRCA2 mutation carriers. They also reported that it is causally related to germline BRCA1/2 mutation because the increased risk cannot be fully explained by a history of hormone therapy treatment (18). Tamoxifen could increase the risk of endometrial cancer in postmenopausal patients, but not the case in premenopausal patients (20).

In our case, breast cancer and endometrial cancer could be diagnosed by pathological analyses. However, it was difficult to make a definitive diagnosis of whether the pancreatic tumor was a primary or metastasis from pathological analysis alone. Therefore, our patient was diagnosed with primary pancreatic cancer by clinical features and the response to treatment of pancreatic cancer. In case of difficulty in diagnosis by the site of the tumor lesion and pathological analysis, the appropriate diagnosis and precise treatment could be possibly decided through multidisciplinary discussions.

The problems in treating MPMNs are the priority of treatment and the extent to which cure is sought. Factors that determine the order of treatment include the progress speed and status of each cancer, the invasiveness of the surgery, and the patient’s general condition. In cases where simultaneous treatment is difficult, the treatment of cancer that determines the prognosis should be given the highest priority. In our case, since the patient’s general condition was good when breast and endometrial cancers developed, surgery could be performed. However, at the time of the onset of pancreatic cancer, the patient had multiple metastases of breast cancer and endometrium cancer, therefore; systemic therapy rather than local therapy was chosen as a treatment.
In the future, the incidence of cancer is expected to increase further with the aging society. New screening tools are needed for the early detection of second and third primary tumors in the risk groups for the development of MPMNs. Research is also needed in developing the proper treatment and tools to follow-up these patients. It is expected that more genetic research will be conducted in the future. However, gene retrieval needs to be done with caution because it may cause humanitarian problems.

**Conclusion**

We report a rare case of MPMNs and discuss the nature, pathogenesis, genetic factor, and therapeutic points of the MPMNs. As life expectancy increases, the number of MPMNs is expected to increase further, and accordingly, early diagnosis and treatment, including gene search for MPMNs, will increasingly become an important issue. Since BRCA pathogenic variant has been reported to link with several type of cancers and at a younger age, it should be recognized that such patients have the potential to develop MPMNs, especially in young patients. Communication with other professions is also important to provide precise treatment at each time.

**Abbreviations**

DCIS, ductal carcinoma in situ; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; MPMNs, multiple primary malignant neoplasms; PR, progesterone receptor.

**Declarations**

**Ethics approval and consent to participate:** Consent was obtained from the patient for participation in this study.

**Consent for publication:** We obtained the patient's consent for publication of this case report.

**Availability of data and materials:** Not applicable.

**Competing interests:** The authors declare that they have no competing interests.

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**Authors’ contributions:** M.O. researched the literature and wrote the manuscript. T.K., S.Y., and S.F. contributed to be involved in the pathological diagnosis of the patient. A.Y., A.K., N.K., Y.I., and I.E. contributed to the manuscript review. All authors read and approved the final manuscript.

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**References**


Figures

Figure 1

Histopathological results. Pathological analysis of surgical tissue from (A) breast, (B) uterus, and (C) abdominal tumor.

Figure 2

Abdominal CT images. CT revealed multiple abdominal mass.
Figure 3

Examination results for mass in her thoracic cavity. Examination for mass in her thoracic cavity by (A) CT, (B) PET-CT (SUVmax = 2.5), and (C) pathological analysis.
Figure 4

PET-CT images. PET-CT showed tumors in pancreas and liver (SUVmax = 4.0 and 4.6, respectively).

Figure 5

Pathological analysis of pancreatic tumor tissue.
**Figure 6**

Transition graph of tumor markers (CA19-9, SPAN-1, and DUPAN-2).

**A. Synchronous vs. Metachronous**

**B. Breast cancer onset timing**

**C. Comorbid cancer**

**Figure 7**

Distribution of MPMNs with breast cancer patients. (A) Synchronous vs Metachronous, (B) Breast cancer onset timing, and (C) comorbid cancer.