A Patient With Metastatic Breast Cancer 15 Years After Bilateral Prophylactic Total Mastectomy and Oophorectomy

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Introduction

It is estimated that 5%–10% of breast cancer is hereditary with 60%–70% of those arising from a Breast Cancer gene mutation in clinical practice (BRCA)1 or BRCA2 mutations.1 Women with BRCA1 or BRCA2 mutations have a 55%–85% lifetime risk of invasive breast cancer. Among women with BRCA1, 36%–63% develop ovarian cancer and among patients with BRCA2 10%–27% develop ovarian cancer.2 BRCA1-related breast cancers tend to be of the basal subtype, with predominant lymphocytic infiltration, and are often more aggressive and associated with negative prognostic factors. They are usually Estrogen (ER)/Progesterone (PR)/HER2neu negative.3 BRCA2-related breast cancers tend to be of the luminal type, and are usually ER/PR positive.4 The median age of breast cancer onset ranges from 40 to 50 years in BRCA1 and BRCA2 carriers compared with 60–70 years in sporadic cases.5,6

Case Report

We report the striking case of a 60-year-old woman who presented with extensive bone metastasis and carcinomatous meningitis of breast cancer origin, 15 years after prophylactic total bilateral mastectomy and oophorectomy.

The patient is a 60-year-old woman who underwent prophylactic total bilateral mastectomy and oophorectomy at the age of 45 after her twin sister was diagnosed with breast cancer in the presence of the BRCA2 mutation. Pathologic examination of the patient’s breasts and ovaries was benign. She was in excellent health for 15 years until she presented with new onset low back pain. On physical examination, she had mild tenderness on palpation of the spine, and had no palpable chest masses or lymphadenopathy. A magnetic resonance imaging (MRI) scan of the spine showed cervical, thoracic, and lumbar enhancement with mottled appearance. Laboratory workup revealed a normal serum protein electrophoresis and free light chains that were within normal limits. She has had a normal colonoscopy a year before presentation. Tumor markers revealed an elevated carcinoembryonic antigen at 36 ng/mL (normal, < 3 ng/mL), and elevated Cancer Antigen (CA)27–29 at 617 U/mL (normal, < 38 U/mL) and a normal CA125. A computed tomography scan of the chest, abdomen, and pelvis revealed no abnormality except for diffusely mottled appearance of the osseous structures (Figure 1). Two days later, the patient presented to our emergency department with...
severe headache, nausea, and vomiting. An MRI scan of the brain revealed bilateral calvarial and clival lesions, along with evidence of mild hydrocephalus and transependymal cerebrospinal fluid seepage concerning for metastatic bone metastasis and leptomeningeal carcinomatosis (Figure 2). Cytology of the cerebrospinal fluid derived from a lumbar puncture was positive for metastatic carcinoma.

A bone marrow core biopsy showed tumor cells that were Mok 6 and CK7 positive, negative for chromogranin, synaptophysin, CD 56, CD 10, RCC, and CK20; ER positive at > 90%, and PR positive at 70%, suggestive of metastatic carcinoma of breast primary (Figure 3). Fluorescence in situ hybridization analysis for HER-2 neu was negative.

The patient underwent intrathecal chemotherapy with weekly methotrexate for 8 consecutive weeks with persistent positive cytology. Fifteen additional doses of weekly intrathecal thiopeta were administered. Her treatment currently consists of an aromatase inhibitor and zoledronic acid. She is clinically doing well and is symptom-free, 16 months after her diagnosis.

Discussion

With the increasing use of genetic testing, more women at high risk are identified and there are no set guidelines on the ideal management strategy for patients who carry the BRCA mutations. Current options include close surveillance, mastectomy, oophorectomy, mastectomy and oophorectomy, and/or chemoprevention.

A randomized clinical trial comparing these options is not feasible for obvious ethical considerations. It is estimated that approximately 50% of BRCA mutation carriers chose bilateral prophylactic mastectomy but the data on breast cancer reduction after mastectomy are limited.7 The types of mastectomy include a subcutaneous mastectomy with preservation of the nipple and areola, a total mastectomy which includes removal of the breasts and underlying skin, a modified radical mastectomy which includes a total mastectomy and axillary dissection, and a radical mastectomy which includes a modified radical mastectomy and removal of the pectoralis muscle.

Hartmann et al conducted a retrospective study of 639 women with a family history of breast cancer who underwent a prophylactic mastectomy at the Mayo Clinic between 1963 and 1990.8 Breast cancer developed in 7 women after subcutaneous prophylactic mastectomy. Of those, 6 were confined to the chest wall and 1 presented with metastatic breast cancer to the bones 12 years after the prophylactic mastectomy with no chest wall involvement. However, none of the 64 patients who underwent total mastectomy developed breast cancer. Data from this study suggested that bilateral prophylactic mastectomy is associated with 90% reduction in breast cancer incidence and mortality in women at high risk of breast cancer.
Meijers-Heijboer et al conducted a prospective study of 139 patients with either BRCA1 or BRCA2 mutation who entered the study without breast cancer. Seventy-six of those patients underwent a prophylactic bilateral mastectomy and 63 remained under surveillance. None of the mastectomy patients developed breast cancer, but 8 of the patients who remained under surveillance did develop breast cancer. The authors of the study concluded a 100% risk reduction among patients who underwent prophylactic mastectomy. However, the study was limited by short follow-up with a mean of 2.9 years.

The Prevention and Observation of Surgical Endpoints (PROSE) study was a case control study of 483 female carriers of the BRCA1 or 2 mutations of which 105 underwent prophylactic mastectomy and 368 did not. After a mean follow-up of 6.4 years, 2 of the patients who underwent prophylactic mastectomy developed breast cancer; both had undergone a subcutaneous mastectomy. The first patient had a BRCA2 mutation and developed breast cancer in an axillary node 2 years after mastectomy, and the other had a BRCA1 mutation and developed breast cancer in the residual breast tissue 9 years after the mastectomy. There was a relative breast cancer risk reduction of 95% in women who had undergone prophylactic salpingo-oophorectomy and 90% risk reduction in those who only had a mastectomy with ovaries left intact.

Domchek et al conducted a large prospective study of 2482 patients who were carriers of the BRCA1 or BRCA2 mutation. No breast cancer was identified in the patients who underwent risk-reducing mastectomy. In addition, women who underwent risk-reducing oophorectomy had a lower risk of breast cancer in both BRCA1 and BRCA2 carriers.

Kauff et al conducted a prospective study of 170 patients with BRCA1 or BRCA2 mutations who chose either risk-reducing salpingo-oophorectomy or close surveillance. Breast cancer developed in 3 out of the 98 women who chose salpingo-oophorectomy and in 8 of the 72 women who chose close surveillance.

A case report of a 72-year-old woman who underwent a prophylactic subcutaneous mastectomy 30 years before presentation was published in 1997. This patient was noted to have a right supraclavicular mass and extensive bone metastasis and postmortem examination revealed a mass underneath the nipple. Another case report was published in 2009 of a 28-year-old woman with BRCA1 mutation who underwent a prophylactic total mastectomy and presented 5 years later with a subsectoral mass, biopsy proven to be of breast origin, hinting to the possibility of a tumor arising from residual breast tissue.

To our knowledge, this is the first case report of metastatic breast cancer presenting after total mastectomy and prophylactic oophorectomy with no evidence of primary tumor and the first case report of carcinomatous meningitis as presenting symptom of metastatic breast cancer after prophylactic mastectomy.

Conclusion
In conclusion, our patient is doing well and is responding to letrozole now 16 months after her diagnosis. She received her last intrathecal treatment 4 months ago and is now symptom-free. She is an example of women at high risk of developing breast cancer who was counseled about the significant risk reduction of bilateral prophylactic mastectomy and oophorectomy. However, our case report illustrates that the risk of breast cancer is not completely eliminated by prophylactic surgery and this adds to the complexity of the decision. Total mastectomy seems to provide additional risk reduction of recurrent breast cancer as compared with the older technique of subcutaneous mastectomy. Additional data would be needed to further define the role of various surgical techniques of mastectomy as well as the role of bilateral oophorectomy in prevention of cancer in this very high risk population.

Disclosure
All authors have no conflicts of interest.

References
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