CE Case Report

A Young Woman With Bilateral Breast Cancer: Identifying a Genetic Cause and Implications for Management

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Abstract

Breast cancer is a common manifestation of an underlying genetic susceptibility to cancer, and 5% to 10% of all breast cancers are associated with a germline mutation in a known risk allele. Detection of mutations has implications for targeted screening and prevention strategies for probands, and for genetic counseling and testing of their family members. This report presents a case involving a 35-year-old woman with no family history of breast or ovarian cancer who presented with a palpable right breast lump. Imaging revealed multiple bilateral breast masses and right axillary adenopathy, and core needle biopsies showed invasive ductal carcinoma in both the right and left breast. This report discusses the appropriate genetics evaluation for a patient with bilateral breast cancer at a young age, including testing for mutations in *BRCA1* and *BRCA2*, followed, if negative, by consideration of testing for mutations in *TP53* (Li-Fraumeni syndrome). Given the specialized counseling and testing needs of patients with Li-Fraumeni syndrome, and the implications for targeted screening strategies if a mutation is found, referral to a cancer genetics expert is strongly recommended. (*JNCCN* 2013;11:512–517)

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Describe the rationale for the management methods used in this case presentation.
- Identify implications for management for bilateral breast cancer in young women.

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Case Report

A 35-year-old Iranian woman with a history of a benign renal mass excised at 14 years of age presented with a palpable lump in her right breast. She took no medications and had no family history of breast or ovarian cancer. Review of systems was unremarkable. On physical examination, she was a well-appearing woman. Breasts were symmetric without dimpling or retraction. Her right breast had several palpable masses in the 2- to 3-cm range. Enlarged right axillary lymph nodes were palpable. Examination of her left breast was unremarkable.

Diagnostic mammogram revealed a suspicious cluster of calcifications in the right upper outer and upper inner quadrants, and right axillary adenopathy.

Ultrasound of the right breast showed 8 irregular solid masses, with the largest measuring 2.5 cm at the 12 o'clock position, and enlarged right axillary lymph nodes. In the left breast were 3 solid masses, measuring 6 mm (11 o'clock), 7 mm (2 o'clock), and 10 mm (3 o'clock).

Within the right breast, core biopsy at 12 and 2 o'clock showed invasive ductal carcinoma (IDC), grade 3, with associated high-grade ductal carcinoma in situ (DCIS). Immunohistochemistry analysis (IHC) showed estrogen receptor (ER) 3+ (95%), progesterone receptor (PR) 2 to 3+ (30%), HER2 0, and Ki-67 50%. Core biopsy of the right axilla demonstrated metastatic adenocarcinoma.

Core biopsy of the left breast at 3 o'clock also showed IDC, grade 2/3, with associated high-grade DCIS. IHC showed ER 2+ (60%), PR-negative (0%), HER2 3+, and Ki-67 40%. Biopsy at 2 o'clock showed high-grade DCIS.

The patient underwent bilateral modified radical mastectomy. Pathologic analysis of the right breast revealed 7 cm of multifocal IDC, grade 2, and 7 cm of intermediate-grade DCIS, 0.1 cm from the deep margin. One of 17 lymph nodes was involved, measuring 1.6 cm with extranodal extension.

Pathology of the left breast showed 3 foci of IDC, measuring 0.1, 0.2, and 0.3 cm, respectively, grade 2, and 6 cm of intermediate-grade DCIS, focally abutting the deep margin. One sentinel lymph node (SLN) was removed and was initially thought to be uninvolved, but was later found to have a 1.4-mm micrometastasis.

Surgical staging was pT3 pN1: stage IIIA for the right breast and pT1a pN1mi: stage IIA for the left breast. Further staging with PET/CT, bone scan, and comprehensive laboratory studies showed no evidence of metastatic disease.

Her breast cancer risk factors were as follows: menarche occurred at 13 years of age and she was premenopausal. She had one pregnancy, at 31 years of age, resulting in a healthy child whom she breastfed for 14 months. She took oral contraceptive pills for 3 months. She drank 6 ounces of alcohol per week and smoked 3 to 4 cigarettes per day. The only family history of malignancy was a maternal grandmother who died of lung cancer at an advanced age. She had 4 siblings who were alive and well.

Because of her bilateral breast cancer at a young age, she met NCCN criteria for *BRCA1/2* mutation testing.[1] She underwent appropriate genetic counseling and then *BRCA1/2* mutation testing by full sequencing, which was negative. BRCAnalysis Comprehensive Rearrangement Testing (BART) was also negative. Given her early-onset bilateral breast cancer, she met Chompret criteria for *TP53* mutation testing, elaborated by the French Li-Fraumeni syndrome (LFS) working group in 2001.[1,2] After relevant genetic counseling, full sequencing of *TP53* was performed, and revealed a deleterious mutation at R248W (742 C>T), thus making the diagnosis of LFS.

For adjuvant chemotherapy, she received dose-dense AC (doxorubicin and cyclophosphamide) for 4 cycles given every 2 weeks with growth factor support, followed by dose-dense paclitaxel on the same schedule; trastuzumab was initiated with paclitaxel, for a planned 1-year course. She underwent bilateral chest wall irradiation and right-sided regional lymph node irradiation (this radiation was performed prior to her *TP53* mutation testing). She completed a year of trastuzumab and initiated tamoxifen therapy for a planned 5-year course. She tolerated all of this therapy well.

Given her diagnosis of LFS, she is participating in a clinical trial to identify novel screening approaches for these patients. This screening program consists of whole-body MRI (including dedicated brain MRI), skin examination, urine cytology annually, and comprehensive laboratory studies, including metabolic panel, CBC, and thyroid function studies every 4 months.[1,3] Her parents and siblings, who live in Iran, were unable to be tested for this same *TP53*

mutation. Her 5-year-old daughter underwent genetic testing shortly after the patient did, and was found to not have the *TP53* mutation. The absence of family cancer history is suggestive (although not conclusive, given the inability to test relatives in Iran) of a de novo mutation, which the patient was the first in her family to have. The patient continues to do well 18 months later, and remains without evidence of recurrent breast cancer or a new primary cancer.

Discussion

This case highlights several important concepts for the diagnosis and management of hereditary breast cancer, including indications for genetic testing, cancer screening for individuals with LFS, and the molecular pathology and treatment of LFS-associated breast cancer.

The presence of bilateral primary breast cancers in a patient, particularly at a young age, is suspicious for an inherited genetic cause. In total, 5% to 10% of breast cancers are caused by germline mutations, most commonly mutations in the *BRCA1/2* genes, which confer substantially elevated risks of developing both breast and ovarian cancer.[4,5] Breast cancer is also a common feature of LFS and Cowden syndrome, which is caused by *PTEN* mutations.[6]

For patients with bilateral breast cancer, at least one of which occurred at age younger than 50 years, clinical genetic counseling and testing for *BRCA1/2* mutations are recommended according to NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Genetic/Familial High-Risk Assessment: Breast and Ovarian (Table 1; to view the most recent version of these guidelines, visit NCCN.org).[1] If a patient in her 30s or younger with breast cancer tests negative for a *BRCA1/2* mutation, then genetic counseling and testing for *TP53* should be considered. *TP53* germline mutations, resulting in LFS, are estimated to account for 5% to 7% of all patients with very-early-onset breast cancer (occurring in the 20s or early 30s).[7,8] Women with LFS have a greater than 90% lifetime risk of cancer,[9] and most commonly develop sarcomas (bone and soft tissue), premenopausal breast cancer, acute leukemia, brain tumors, adrenocortical carcinoma, choroid plexus carcinoma, colon and pancreatic cancer, or melanoma.[7,10,11] Individuals may meet criteria for *TP53* testing, even in the absence of a suggestive family history, because of the possibility of de novo mutations (Chompret criteria).[1,2] Additional testing criteria are based on personal and family history of various LFS-associated cancers, often including a young age of onset (Table 1).

Based on recent reports, *TP53*-associated cancers are more likely to exhibit a triple-positive phenotype (estrogen- and progesterone-positive and HER2-amplified),[12–14] as was the case for this patient's left-sided breast cancer. The presence of a triple-positive breast cancer in a young woman adds to the indication for genetic testing for germline *p53* mutations, even without a family history for breast or other cancers. The fact that this patient had discordant molecular pathologies for HER2 amplification suggests that these were 2 separate primary breast cancers, consistent with the underlying diagnosis of LFS.

The diagnosis of a *TP53* mutation has implications for both the proband and her family. Confirmation of a cancer predisposition gene mutation may prompt several normal emotional reactions. Distress, grief, anger, and fear are not uncommon feelings in adjusting to this new diagnosis, and further peer or professional counseling resources should be made available as needed. For the family members of a patient with a confirmed *TP53* mutation, presymptomatic testing of at-risk relatives allows identification of carriers who need close monitoring, given that the estimated lifetime risk of developing cancer is 73% for men and 93% for women with LFS.[9]

An individual with a cancer-predisposition gene mutation that follows an autosomal dominant inheritance pattern, such as *BRCA1/2* or *TP53*, has a 50% chance of passing the mutation to each child. If neither parent is a carrier, testing of siblings is still recommended to exclude the small risk of gonadal mosaicism (estimated at 1%). *TP53* mutation testing is available to minors because tumor risk may be present in childhood and a positive result would alter screening recommendations. Although the patient's daughter did not inherit her mother's *TP53* mutation, future children would still have a 50% chance of inheriting the mutation. For couples desiring children, options for prenatal diagnosis and assisted reproduction, including preimplantation genetic diagnosis, should be discussed.[15]

The broad tumor spectrum associated with *TP53* mutations poses a challenge in terms of early detection and prevention. Although data on effectiveness

Table 1 NCCN Guidelines for *BRCA1/2* and *TP53* Mutation Testing Recommendations

***BRCA1/2* Mutation**	***TP53* Mutation**
Individual from a family with a known deleterious *BRCA1/BRCA2* mutation	• Individual from a family with known *TP53* mutation[26]
Personal history of breast cancer: • Diagnosed age ≤45 y • Diagnosed any age with ≥1 close relative with breast cancer ≤50 y and/or ≥1 close blood relative with epithelial ovarian cancer at any age • Two breast primaries when first breast cancer diagnosis at age ≤50 y • Diagnosed age ≤60 y with a triple-negative breast cancer • Diagnosed age ≤50 y with a limited family history • Diagnosed at any age with ≥2 close blood relatives with breast cancer at any age • Diagnosed at any age with ≥2 close blood relatives with pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age • Close male blood relative with breast cancer • High-risk ethnicity, such as Ashkenazi	• Classic Li-Fraumeni syndrome (LFS) criteria: ➤ Combination of individual diagnosed age <45 y with a sarcoma AND A first-degree relative diagnosed age <45 y with cancer AND additional first- or second-degree relative in same lineage with cancer diagnosed age <45 y, or sarcoma at any age • Chompret et al[2,8] criteria ➤ Individual with a tumor from LFS tumor spectrum (eg soft tissue sarcoma, osteosarcoma, brain tumor, breast cancer, adrenocorticoid carcinoma, leukemia, lung bronchoalveolar cancer) before age 46 y, AND at least one first- or second-degree relative with any of the aforementioned cancers (other than breast cancer if proband has breast cancer) younger than 56 y or with multiple primaries at any age OR ➤ Individual with multiple tumors (except multiple breast tumors), 2 of which belong to LFS tumor spectrum with the initial cancer occurring before the age of 46 y OR ➤ Individual with adrenocortical carcinoma or choroid plexus carcinoma[7,8] at any age, regardless of family history
Personal history of epithelial ovarian cancer	
Personal history of male breast cancer	
Personal history of pancreatic cancer or aggressive prostate cancer (Gleason score ≥7) at any age with ≥2 close blood relatives with breast and/or ovarian and/or pancreatic or aggressive prostate cancer (Gleason score ≥7) at any age	
Family history only and reasonable likelihood of mutation based on clinical judgment	• Breast cancer at age ≤35 y with a negative *BRCA1/2* mutation test

are limited, the following clinical surveillance guidelines are provided by NCCN. Annual comprehensive physical examinations, including careful neurologic and skin examinations, are recommended.[1] Breast cancer screening includes self-breast examination, clinical breast examination every 6 to 12 months, annual mammogram, and breast MRI starting at age 20 to 25 or individualized based on the earliest onset of breast cancer in the family. Discussion of risk-reducing mastectomy versus continued intensive surveillance is recommended on a case-by-case basis. Because colon cancer has recently been associated with LFS, screening colonoscopy is recommended by age 25 years, to be repeated every 2 to 5 years. Patients with LFS should also be educated regarding signs and symptoms of cancer. Targeted surveillance should also be incorporated based on individual family histories.

Efforts to improve on current screening guidelines are underway. The long-term risk for second malignancies from radiation exposure in individuals with *TP53* mutations argues for using non–radiation-based screening methods. NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian recommend that clinicians discuss the option to participate in clinical trials studying novel screening approaches using technologies, when possible (to view the most recent version of these guidelines, visit NCCN.org). A consortium of experts at several academic institutions has developed a screening protocol as part of a clinical trial for patients with LFS that includes annual rapid whole-body MRI, annual head MRI, annual bilateral breast MRI for women, annual CBC, comprehensive metabolic panel, and thyroid function studies.[3] Melanoma and colon cancer screening are also incorporated according to standard guidelines.

The consortium is collecting outcomes data from this screening protocol to inform future research and clinical practice. An initial prospective study of 8 fam-

ilies of asymptomatic *TP53* mutation carriers demonstrated that early cancer detection and survival rates were improved among those who participated in the screening protocol (n=18) compared with those who did not (n=16).[3] In the screened group, 10 neoplasms were identified, 5 of which were malignant. All of these cancers were resected, and the patients remained without evidence of disease through the follow-up period. In the unscreened group, 10 of 16 mutation carriers developed cancer, and only 2 of these 10 survived. In addition to efficacy, this study demonstrated feasibility of the protocol: all patients in the screening group were fully compliant with the protocol and none withdrew. These data, although preliminary, provide support for genetic testing and comprehensive presymptomatic surveillance in LFS. As the understanding of genetic testing results increases and other risk modifiers emerge, screening strategies may be further refined and tailored to individual patients.[16–20] Recent work has identified a *TP53* founder mutation of high frequency (approximately 5% of patients with breast cancer) in Southern Brazil; although some uncertainty remains about the penetrance of this mutation and associated cancer risk, *TP53* genetic testing may be of particular relevance in patients of Brazilian ethnicity who have breast cancer.[21,22]

The role of *TP53* mutations in determining systemic therapies with DNA-damaging chemotherapeutic agents or radiation therapy for LFS with cancer is controversial and difficult. Certainly, the biologic function of the *p53* gene in the DNA damage response pathway suggests that individuals with *TP53* mutations may be more sensitive to the carcinogenic effect of DNA-damaging drugs and ionizing radiation, consistent with clinical observation.[9,11,23–25] Accordingly, NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian recommend that therapeutic radiation be used with caution in these patients (to view the most recent version of these guidelines, visit NCCN.org). A challenge in clinical practice is that *TP53* test results may not be available at the time of adjuvant therapy, as occurred in the present case. A genetics evaluation may take a substantial amount of time, particularly if the patient has no history that is highly suspicious for LFS, in which case testing usually begins with *BRCA1/2*. If a high suspicion for a *TP53* mutation exists that may impact treatment strategies, then genetics evaluation should be expedited if possible, and mastectomy may be considered as a way to potentially avoid adjuvant radiation.

Despite the need to use caution with DNA-damaging therapies in LFS, the high risk for recurrence of cancers, such as in the case of this patient, argues for the use of highly effective adjuvant treatment. When a patient is known to carry a *TP53* mutation, the authors generally support using chemotherapy per the standard of care, but consider holding radiation therapy unless necessary for short-term benefit.

The familial, psychological, screening, and treatment implications of LFS are complex. Referral to an expert cancer genetics program for genetic counseling, testing, and management recommendations is strongly encouraged.

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Posttest Questions

1. True or False: 5% to 10% of breast cancers are caused by germline mutations, most commonly mutations in the *BRCA1/2* genes, which confer substantially elevated risks of developing both breast and ovarian cancer.
2. True or False: An individual with a cancer-predisposition gene mutation that follows an autosomal dominant inheritance pattern, such as *BRCA1/2* or *TP53*, has a 95% chance of passing the mutation to each child.
3. True or False: The long-term risk for second malignancies from radiation exposure in individuals with *TP53* mutations argues for using non–radiation-based screening methods.