Chest Wall Leiomyosarcoma After Breast-Conservative Therapy for Early-Stage Breast Cancer in a Young Woman With Li-Fraumeni Syndrome

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Abstract

Li-Fraumeni syndrome (LFS) is one of the most penetrant forms of familial cancer susceptibility syndromes, characterized by early age at tumor onset and a wide spectrum of malignant tumors. Identifying LFS in patients with cancer is clinically imperative because they have an increased sensitivity to ionizing radiation and are more likely to develop radiation-induced secondary malignancies. This case report describes a young woman whose initial presentation of LFS was early-onset breast cancer and whose treatment of this primary malignancy with breast conservation likely resulted in a secondary malignancy arising in her radiation field. As seen in this case, most breast cancers in patients with LFS exhibit a triple-positive phenotype (estrogen receptor–positive/progesterone receptor–positive/HER2-positive). Although this patient met classic LFS criteria based on age and personal and family history of cancer, the NCCN Clinical Practice Guidelines in Oncology for Genetic/Familial High-Risk Assessment: Breast and Ovarian Cancer endorse genetic screening for *TP53* mutations in a subset of patients with early-onset breast cancer, even in the absence of a suggestive family history, because of the potential for de novo *TP53* mutations. (*JNCCN* 2012;10:939–942)

Li-Fraumeni syndrome (LFS) is one of the most penetrant forms of familial cancer susceptibility syndromes, characterized by an early age of tumor onset and a wide spectrum of malignant tumors. Patients with *TP53* mutations are predisposed to develop sarcomas, early-onset breast cancer, brain tumors, leukemia, and adrenocorti-

cal carcinomas.^{1,2} The lifetime risk of cancer in these patients is extraordinarily high with 50% of patients having a diagnosis of cancer by the age of 30 and 90% by the age of 50.³ Identifying LFS in patients with cancer is clinically imperative because these patients have an increased sensitivity to ionizing radiation and are more likely to develop radiation-induced secondary malignancies.^{4–7} This case report describes a young woman whose initial presentation of LFS was early-onset breast cancer and whose subsequent treatment with breast conservation likely resulted in the rapid development of a secondary malignancy arising in her radiation field.

Case Report

A 24-year-old female presented after incidentally palpating a mass in the superior aspect of her left breast. Biopsy of the mass revealed invasive ductal carcinoma. She underwent a lumpectomy with axillary node dissection and was found to have a 2.7-cm moderately differentiated invasive ductal carcinoma that was estrogen receptor–positive/progesterone receptor–positive/HER2-positive (ER+/PR+/HER2+) on immunohistochemistry. Lymph node dissection was negative in 0 of 23 nodes. Surgical margins were negative. Imaging revealed no evidence of metastasis. She received adjuvant chemotherapy with 4 cycles of doxorubicin and cyclophosphamide, followed by 4 cycles of paclitaxel with concurrent trastuzumab. She underwent photon irradiation using an opposed tangent technique, which delivered 50.4 Gy in 28 fractions to the whole breast, followed by a 10-Gy boost to the lumpectomy cavity. She was then lost to follow-up and did not receive the intended course of adjuvant tamoxifen nor the recommended full year of trastuzumab therapy.

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Twenty-seven months after completing adjuvant radiotherapy, she presented with blurry vision that rapidly progressed to right eye blindness. Brain MRI showed right globe enhancement concerning for choroidal metastasis. She had no parenchymal brain lesions. A PET/CT showed a new 4 x 3-cm left chest wall mass involving the serratus anterior muscle, extensive left breast skin thickening, bilateral pulmonary nodules, and enlarged cervical and mediastinal lymph nodes (Figure 1).

The patient received urgent radiation therapy to the right orbit to a dose of 40 Gy in 16 fractions and was started on tamoxifen and trastuzumab for presumed metastatic breast cancer. A CT-guided biopsy of the chest wall mass revealed a high-grade soft tissue spindle cell neoplasm consistent with leiomyosarcoma (Figure 2). Review of her prior radiation therapy fields showed the left chest wall mass to be within the prior radiotherapy field (Figure 3). Biopsy of a lung nodule, however, was consistent with metastatic breast cancer.

The patient had an extensive family history of cancer (Figure 4). Although she had previously tested negative for *BRCA1* and *BRCA2* germline mutations, she met the classic LFS criteria, including a diagnosis of sarcoma before age 45 years and a family history of early-onset (< 40 years of age) of malignancy in 2 maternal aunts and her paternal grandmother.⁸ After her diagnosis of leiomyosarcoma, the patient underwent genetic evaluation

and tested positive for a germline mutation in *TP53* (14525G>T; glu286stop), confirming a molecular diagnosis of LFS.

Discussion

Although breast cancer is the most frequent neoplasm in women with *TP53* mutations, it is less commonly the first presentation of LFS. The first clinical report of breast cancer as a primary presentation found 8 cases among 43 families with known LFS.⁹ The infrequency of LFS in the general population and the rarity of breast cancer as a primary presentation makes the diagnosis of LFS difficult in patients with early-onset breast cancer. In all patients with early-onset breast cancer, only an estimated 5% to 7% of cases can be attributed to a mutation in *TP53*.^{2,10}

Despite the relative rarity of this diagnosis, this case highlights the clinical importance of considering diagnostic testing for *TP53* mutations in patients with early-onset breast cancer at diagnosis. Locoregional management recommendations for these patients may be significantly influenced if LFS is detected, because the *TP53* mutation confers an increased sensitivity to ionizing radiation, resulting in an increased frequency of radiation-induced secondary malignancies.⁴⁻⁷ Young patients are statistically more likely to choose breast conservation therapy with lumpectomy followed by adjuvant radiation therapy.¹¹ Patients with LFS syndrome, however, are

Figure 1 CT thorax with a left chest wall mass arising from the serratus anterior muscle (arrow).

Figure 2 Spindle cell lesion with hyperchromatic, pleomorphic nuclei with increased mitotic activity. Desmin/actin positive; p63/S100/CD31/CD34 negative. Hematoxylin-eosin, original magnification x400.

Secondary Malignancy in a Patient With Li-Fraumeni Syndrome

Figure 3 Isodose distribution of left breast irradiation.

cautioned to avoid radiation therapy when possible and may be advised to pursue mastectomy.^{12,13}

In the general population, radiation-induced malignancies are rare and usually occur 10 or more

years after radiation therapy.¹⁴ Even in patients with LFS, the earliest latent period to develop a second malignancy after irradiation is generally considered to be 4 years.^{15,16} The patient in this case developed a secondary malignancy only 2 years after the completion of whole breast radiation therapy, representing one of the shortest reported latent periods to secondary malignancy in a patient with LFS.

Because of the expense and psychosocial stress associated with genetic testing, screening all patients with early-onset breast cancer for LFS generally has not been recommended, except in those who have a compelling family history.¹⁷ Concern exists, however, that patients are being missed by this standard practice.¹⁸ In one study of women with early-onset breast cancer who tested negative for *BRCA1* and *BRCA2* mutations, 4% tested positive for a *TP53* mutation who had no family history of cancer at all.¹⁰ Because of the possibility of de novo *TP53* mutations, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Genetic/Familial High-Risk Assessment: Breast and Ovarian Cancer

Figure 4 Pedigree.

Abbreviations: ca, cancer; d, age at death; dx, age at diagnosis; ER, estrogen receptor; PR, progesterone receptor.

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recommend TP53 testing for individuals with multiple primary tumors, 2 of which belong to the LFS tumor spectrum (ie, sarcoma, breast cancer, adrenocortical carcinoma, brain tumor, leukemia, lung bronchoalveolar cancer) with initial cancer diagnosed at younger than 36 years regardless of family history, and in individuals diagnosed with breast cancer at younger than 30 years who have a negative *BRCA1* and *BRCA2* test (to view the most recent version of these NCCN Guidelines, visit NCCN.org).¹⁷ The NCCN Guidelines also recommend genetic counseling for patients who are considering p53 testing.¹⁷ A multidisciplinary approach with professional geneticists, counselors, psychologists, and oncologists may improve patient understanding of the risks and benefits associated with genetic testing.¹⁹

Research now indicates that most breast cancer in patients with LFS exhibits a “triple-positive” phenotype (ER+/PR+/HER2+).^{20–22} Although family history alone may not be enough to detect all patients with LFS, a thorough family history, attention to tumor histology, and a high level of clinical suspicion may allow physicians to identify and optimize therapy for their LFS patients and minimize the potential late effects associated with this syndrome.

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