

Hereditary Inflammatory Breast Cancer Associated With BRCA2 Mutation: A Rare Disease Presentation in Mother and Daughter

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Case Report

A 40-year-old white woman of Irish descent presented with a 4-week history of a right breast mass associated with edema and enlargement of the breast. Her family history was significant for inflammatory breast cancer (IBC) in her mother, who was diagnosed and died at age 35, as well as for breast cancer in a paternal aunt diagnosed at age 55. On physical examination, she had an enlarged right breast with a palpable 9 cm mass in its inferolateral aspect, with *peau d'orange* skin changes around the right nipple (Figure 1) and associated ipsilateral axillary lymphadenopathy. Her left breast was unremarkable. Diagnostic ultrasound (Figure 2) showed an irregular 5-cm mass at the 9 o'clock position, bilateral nodular tissue densities seen throughout both breasts, and right axillary adenopathy. Thickened dermis was noticed in the periareolar area and the inferior aspect of the right breast. A core biopsy of the right breast mass revealed a grade III, infiltrating ductal carcinoma with associated high-grade ductal carcinoma in situ (DCIS). The tumor was estrogen receptor (ER)-positive (80%) and negative for progesterone (PR), human epidermal growth factor receptor 2 (HER2), and epidermal growth factor receptor (EGFR). A single-site skin punch biopsy did not show invasion of the dermal lymphatics; however, given the constellation of findings and the typical course, the clinical diagnosis of inflammatory breast cancer was made. A staging positron emission tomography (PET) scan demonstrated increased uptake in the right internal mammary, right paratracheal, and cervical lymph nodes. A biopsy of the paratracheal lymph node confirmed the presence of breast cancer metastasis.

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Figure 1. Inflammatory breast cancer (IBC) of right breast. The enlarged right breast has significant edema.

Given the patient's personal and family history, genetic testing for breast cancer predisposition was recommended. Full sequencing of *BRCA1* and *BRCA2* genes was positive for a suspected deleterious mutation in the *BRCA2* gene, S2670L (8237C>T). This mutation results in the substitution of leucine for serine at amino acid position 2670 of the *BRCA2* protein. This genetic alteration in the *BRCA2* gene had been previously considered a variant of undetermined significance (VUS). However, numerous observations enabled Myriad Genetic Laboratories to reclassify this mutation as suspected deleterious, based on its strong association with more severe, personal and family history that is typical for individuals with deleterious *BRCA2* mutations.^{1,2} This re-classification agrees with the structure-based prediction previously made by Karchin and associates.³ Because the patient pursued treatment at an outside institution closer to her home, details regarding further diagnostic work-up or treatment are not currently available.

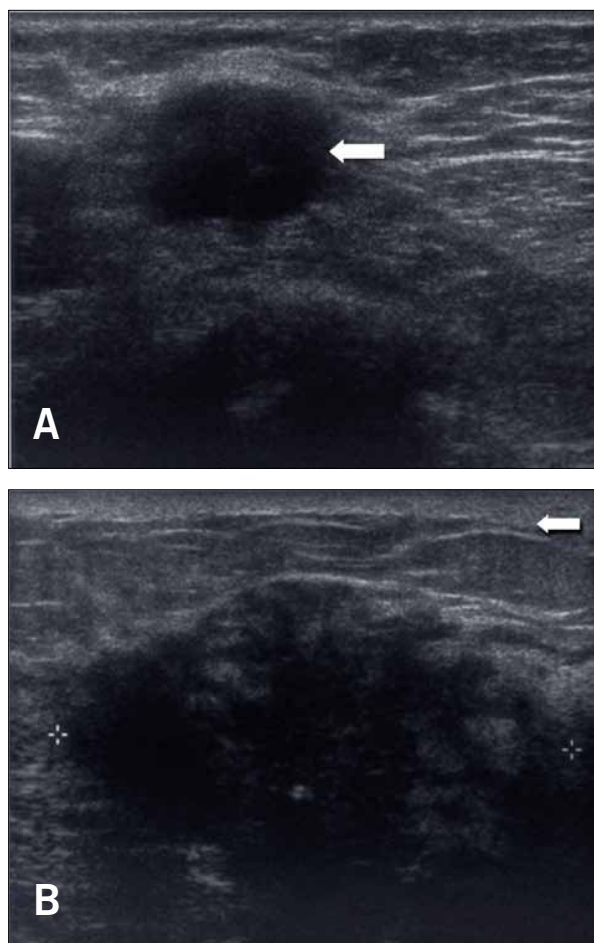


Figure 2. A. Enlarged axillary lymph node with replaced fatty hilum and irregular cortex (arrow). B. 5-cm irregular mass of heterogeneous echo texture with associated vascularity (between asterisks) and overlying thickened dermis (arrow).

Discussion

IBC is a rare and aggressive form of breast cancer that accounts for 1–3% of all breast cancer diagnoses.⁴ Although its incidence is low, it is rising, unlike that of non-IBC.⁵ Clinically, IBC is characterized by rapid progression, aggressive clinical behavior,⁶ and earlier age at diagnosis. Despite the introduction of primary chemotherapy and multimodality treatment, it is often a lethal disease, primarily because of its strong metastatic potential; its 3-year survival ranges from 32–42%, and the median overall survival (OS) is 3.8 years.⁷

Because of its rarity, data regarding risk factors for IBC are scant, and it remains unknown if these risk factors are the same as for non-IBC. Currently, there are a few recognized risk factors for IBC; factors with the strongest association include African-American ethnicity, high body mass index (BMI), and younger age at disease onset.

In addition, very few studies have evaluated the presence of a familial link for IBC. Traditionally, IBC has been considered a *de novo* (sporadic) malignancy, rather than a familial or hereditary malignancy, and *BRCA* testing is not routinely recommended in patients with IBC.

In 2007, Bondy and colleagues⁸ established a multinational IBC registry to identify risk factors and prognostic features by prospectively collecting epidemiologic, clinical, and imaging data from IBC patients. As of early 2010, 85 patients had been enrolled, with younger age (median, 55 years) and high BMI (50% of patients above 30) being identified as probable risk factors.

Although less than 10% of breast cancer cases are hereditary,⁹ with only a fraction of those attributable to inherited mutations in *BRCA1* or *BRCA2* genes,¹⁰ a true familial link for IBC has not been evaluated in large, epidemiologic studies. A small case-control study by Aziz and coworkers¹¹ suggested that a family history of breast cancer was more prominent in IBC compared to non-IBC (20% vs 5%, respectively). A recently reported, retrospective study evaluated the incidence of *BRCA* mutations in women with IBC.¹² In this study, which investigated differences in the *BRCA* mutation rate between IBC and non-IBC patients, 992 patients with non-IBC and 39 patients with IBC underwent genetic testing; epidemiologic, clinical, and pathologic features were reviewed. Although IBC affected patients of slightly younger age (40 years for IBC vs 42 years for non-IBC), there was no statistically significant difference in the rate of *BRCA1* and *BRCA2* mutations between cohorts (35.9% in IBC patients vs 26.1% in non-IBC patients; $P=.169$). Therefore, the authors recommended applying standard *BRCA* testing guidelines to women with IBC.

Although IBC has been reported in conjunction with *BRCA1* and *BRCA2* mutations and in conjunction with family history of breast cancer, to our knowledge, this is the first reported case of IBC in the same family, and specifically, in a mother and daughter. Our case is not only unique because of the hereditary IBC presentation, it is also linked to a suspected deleterious *BRCA2* mutation. Due to the rarity of both IBC and *BRCA* mutations, it would be difficult to collect data on a larger series to validate any causal relationship. Nonetheless, the small studies cited above and this observation point to a potential common genetic mechanism underlying the development of IBC and non-IBC, with possibly a few additional genetic aberrations in IBC that lead to its unusually rapid and aggressive course.

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Review

Deleterious BRCA2 Mutation in a 40-Year-Old Woman With Inflammatory Breast Cancer and Strong Family History of Maternal Inflammatory Breast Cancer at a Young Age

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Introduction

Jimenez and associates present and discuss a very intriguing case of a 40-year-old white woman of Irish heritage who presented with an inflammatory, invasive, estrogen receptor (ER)-positive, progesterone (PR)-negative, human epidermal growth factor receptor 2 (HER2)-negative right breast cancer, and whose mother had succumbed to the disease at age 35.¹ Because of this familial significance, which further included a paternal aunt diagnosed with breast cancer at age 55, the proband met the standard criteria for testing for mutations in *BRCA1* or *BRCA2*. Indeed, she was found to harbor a deleterious sequence in *BRCA2* of S2670L (8237C>T),

reclassified after family studies by the genetic laboratory from a previous characterization of a mere variant of undetermined significance (VUS).

The patient presented with inflammatory features of the breast mass, and was subsequently shown to have developed metastatic disease, with the rapid appearance of her breast mass heralding an aggressive behavior of this cancer. This is an important report of a deleterious *BRCA* mutation in a woman with inflammatory breast cancer (IBC), itself a rare form of breast cancer. Due to *BRCA2*-positivity, the patient would be routinely counseled on her simultaneous increase of contralateral breast cancer and ovarian cancer, with appropriate risk reduction strategies considered.^{2,3} However, considering her presentation with IBC, oncologists should also be made aware of the need to regard this entity as an additional manifestation of hereditary breast cancer.

Discussion

On account of the increasing incidence of *BRCA* mutations in other types of breast cancer (particularly [preinvasive] ductal carcinoma in situ⁴ [DCIS] and specific invasive breast cancers, such as the triple-negative phenotype^{5,6}), the standard National Comprehensive Cancer Network (NCCN) Guidelines for offering risk evaluation and testing have expanded to include these among the high-risk criteria.² Included within the well-described case presentation and review of the current literature by Jimenez and colleagues is a recent abstract by Gutierrez-Barrera and coworkers,⁷ which raises the question as to whether IBC should also be included in the well-recognized criteria for individuals who could also be at high risk for hereditary breast and ovarian cancer syndrome (HBOC).

This presentation of such an aggressive breast cancer in a young woman at familial high risk brings forth many

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other questions. The biology of her tumor, while ER-positive, is an intriguing point of study in the quest to define specific chemosensitivity patterns of IBC. Several ongoing studies and clinical trials are trying to identify such patterns, and are looking at specific microRNA and gene array signatures that not only set IBC apart as a distinct entity of breast cancer, but also may even define particular markers as therapeutic drug targets.⁸⁻¹¹ Specifically, the p53 tumor suppressor pathway in IBC is being examined as a potential explanation of aggressive behavior in IBC¹² and as a potential target for therapeutic intervention.

Conversely, since *BRCA* deficiency correlates with inhibition of DNA polymerase and defects in DNA repair, and because highly proliferative IBC may be exquisitely chemosensitive, this begs the question as to whether specific inhibitors of DNA repair may provide a higher rate of response and disease control in IBC versus other more prevalent invasive breast cancers. Studies utilizing poly (ADP-ribose) polymerase (PARP) inhibitors to enhance chemotherapy-induced DNA damage in *BRCA*-mutated breast cancers have done so in the previously treated metastatic setting.¹³⁻¹⁵ We do know that higher complete response (CR) rates have been achieved in ER-negative, *BRCA1*-mutated breast cancers treated in the neoadjuvant setting.¹⁶ Recently, it has also been shown that while of different histology, *BRCA2*-mutated ovarian cancers may actually fare better after treatment than non-mutated ovarian tumors.¹⁷ It will be important to design clinical trials that further focus on the exquisite sensitivity of IBC to chemotherapy, especially those stratified to *BRCA1* or *BRCA2* mutation status, and to gauge endpoints of not only CRs with such possible combinations, but also progression-free survival and overall survival.

Conclusion

Participation in center-based family registries will continue to be essential in identifying new mutations responsible for high-risk situations, as well as performing family linkage analysis. Although standard criteria related to age at diagnosis should certainly prompt genetic testing for a patient at high risk for harboring a *BRCA* mutation by standard prediction models,¹⁸⁻²¹ the inclusion of IBC in the histology of breast cancers that may harbor *BRCA* mutations is further illustrated by this very significant case study.

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