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Occult Primary Breast Cancer at a Comprehensive Cancer Center

Oluwadamilola M. Fayanju, MD, MPHS[1], **Donna B. Jeffe, PhD**[2,3], and **Julie A. Margenthaler, MD**[1,3]

[1]Department of Surgery, Washington University School of Medicine, St. Louis, MO

[2]Division of Health Behavior Research, Department of Medicine, Washington University School of Medicine, St. Louis, MO

[3]The Alvin J. Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine, St. Louis, MO

Abstract

BACKGROUND—Management of occult primary breast cancer (OPBC), i.e., breast cancer that first presents through regional nodal or distant disease without clinical or mammographic evidence of disease in the breast, has been controversial and inconsistent. Here, we review OPBC patients treated at our institution.

METHODS—We conducted a retrospective review of women diagnosed with a first primary breast cancer between March 1999 and September 2010 to identify patients who presented with isolated axillary lymphadenopathy proven to be histologically consistent with primary breast malignancy but had no evidence of a breast mass on physical exam, mammography, or ultrasound. Descriptions of treatments received, recurrence, morbidity, and mortality as of October 2012 are reported.

RESULTS—Of 5533 patients reviewed, 7 patients (0.1%) were identified. Median age was 65 years old (range 40–72), and median length of follow-up was 86 months (range 42–124). Four patients underwent modified radical mastectomy (MRM), 1 patient had a lumpectomy and axillary lymph node dissection (ALND), and 2 patients had ALND without breast surgery. Four patients received adjuvant radiation therapy. All 7 patients received chemotherapy. Three patients received endocrine therapy, and 2 patients received anti-HER2 therapy. At last follow-up, all 7 patients were alive with no evidence of disease.

CONCLUSIONS—While there was some variation in the management of OPBC at our institution, our patients had excellent outcomes following multimodal treatment. Our results support a curative-intent approach to treatment of OPBC and illustrate the need for individualized treatment algorithms based on tumor biology and extent of disease at diagnosis.

Keywords

breast cancer; occult cancer; cancer of unknown primary; axillary lymph node

Corresponding Author. Oluwadamilola Fayanju, MD, MPHS, Campus Box 8109, 660 S. Euclid Ave, St. Louis, MO 63110, USA, fayanju@wustl.edu| *telephone*: (314) 747-2691 | *fax*: (314) 454-7941.

INTRODUCTION

Approximately 0.1–0.8% of all breast cancers is occult,[1–6] i.e., patients present with regional or distant disease (usually axillary lymphadenopathy) that is histologically consistent with a primary breast cancer, but clinical and mammographic evaluation of the breast fails to demonstrate a tumor. Management of occult primary breast cancer (OPBC) has been inconsistent and controversial since its initial description by Halsted in 1907,[7] but the rarity of this form of breast cancer has made it difficult to standardize management. Furthermore, the natural history of OPBC remains unclear: most case series have reported outcomes that are better than those of non-occult breast cancers with similar nodal involvement,[2,3,5,8–14] but a few have reported outcomes that are comparable[1] or significantly worse.[15]

Here, we describe the management and outcomes of OPBC patients treated at our institution, Siteman Cancer Center, a National Cancer Institute (NCI)-designated Comprehensive Cancer Center in St. Louis, Missouri. Our series is the first to include OPBC patients who received anti-HER2 therapy and, reflecting evolutions in diagnosis, a very high proportion of the patients in our cohort received breast magnetic resonance imaging (MRI) as part of their work-up. By reviewing the management and outcome of OPBC patients at Siteman, we hope to elucidate both the benefits and disadvantages associated with a multidisciplinary treatment approach to OPBC.

METHODS

A retrospective review was conducted of women diagnosed with a first primary breast cancer at our institution between March 1999 and September 2010 to identify patients who presented with isolated axillary lymphadenopathy proven to be histologically consistent with primary breast malignancy but who had no evidence of a breast mass on physical exam, mammography, or ultrasound. Women with a prior history of in situ or invasive breast cancer were excluded. Clinical, demographic, and pathological data including age; race; hormone receptor status; results of radiographic and pathological examinations; types of surgical, systemic, radiation, endocrine, and/or receptor-targeted treatments received; and outcome data were retrospectively collected from patients' medical records and Siteman's tumor registry. Follow-up time was calculated from date of diagnosis to date of last hospital visit. Descriptions of treatments received, recurrence, morbidity, and mortality as of October 2012 are reported. Statistical analyses were conducted in SAS 9.2 (SAS Institute Inc., Cary, North Carolina). Prior to commencing this retrospective study, we obtained approval from the institutional review board at our medical center with a waiver of consent.

RESULTS

Of 5533 patients reviewed, seven OPBC patients (0.1%) were identified. Characteristics of these patients are reported in Table 1. Median age was 65 years old (range 40–72), and median length of follow-up was 86 months (range 42–124). Six patients were Caucasian, and one was Asian. Two patients were perimenopausal, and five were postmenopausal. Axillary metastases were poorly differentiated in four patients, for whom histological type (ductal vs. lobular) was not reported. Of the remaining three patients, one was noted to have a mixture of ductal and lobular histology, and two had pure ductal histology. Three patients had estrogen-receptor-positive (ER+) axillary tumors, and two had triple-negative tumors. At time of diagnosis (by surgical pathology), five patients had N1 disease (1–3 lymph nodes with malignant cells), and one patient had N2 disease (4–9 lymph nodes with malignant cells); the original axillary tumor burden of one patient prior to adjuvant chemotherapy was not documented, and no malignancy was found following post-chemotherapy axillary lymph

node dissection (ALND). One patient had a family history significant for breast cancer, and one patient had a history of tobacco use.

Four patients underwent modified radical mastectomy (MRM), one patient had a lumpectomy (despite no radiographic findings in the breast) of the axillary tail of the breast in continuity with ALND, and two patients had ALND without breast surgery. None of the five patients who underwent breast surgery was found to have had an intramammary tumor on pathologic examination. Six patients had breast MRI as part of their pre-treatment workup, and two of these patients' MRIs were interpreted as having foci of enhancement suspicious for cancer; however, neither of these patients underwent second-look imaging and/or subsequent biopsy to further elucidate these findings. Both of these patients underwent breast surgery after receipt of neoadjuvant systemic therapy and their final pathology was benign, so it is unknown whether either of them initially had small foci of intramammary malignancy that receded in response to treatment or whether their MRI results were false positives.

Four patients received adjuvant radiation therapy to the breast/chest wall and nodal basins. All seven patients received chemotherapy: three received only neoadjuvant therapy, two received only adjuvant therapy, and two received both. Three patients received endocrine therapy (tamoxifen or an aromatase inhibitor), and two patients received anti-HER2 therapy (trastuzumab). Two patients experienced adverse sequelae after MRM including lymphedema and upper extremity venous thrombosis, and two patients experienced significant chemotherapy-related side effects including neutropenic fever and pancytopenia with hypotension. Almost three years after her initial diagnosis with triple-negative OPBC, one patient developed a contralateral breast cancer that was successfully treated without evidence of recurrence. There were no locoregional recurrences. None of these patients was diagnosed with a non-breast adenocarcinoma during the course of her follow-up. All seven patients are alive at follow-up without any evidence of disease.

DISCUSSION

In keeping with the findings of recent OPBC case series,[1–3,5,8–14] the OPBC patients at Siteman had excellent outcomes, and a multidisciplinary approach was utilized for all. Four surgeons treated the seven patients in this series, but no two patients received the same course of surgical, systemic, radiation, and receptor-targeted treatment, reflecting the heterogeneity of OPBC treatment reported in recent reviews.[16,17] As with non-occult node-positive breast cancers, lymph node tumor burden is the primary prognosticator for OPBC.[16,17] Thus one would expect OPBC treatment to focus on local control of axillary disease, which was the case for members of our cohort, all of whom underwent ALND. While there is a general consensus that primary treatment of the axilla is necessary in cases of OPBC with axillary presentation, some researchers have suggested that radiation therapy might be a preferable alternative to ALND.[18,19] The necessity of extensive breast surgery, however, is less clear. Reported pathological discoveries of occult breast tumors in OPBC mastectomy specimens range between 45% and 82%.[2,11,18] A recent review reported that 72% of mastectomy specimens from OPBC patients contained an occult malignancy on pathological exam, and the authors of that review supported performing mastectomies in all otherwise healthy patients with OPBC in order to maximize tumor cytoreduction and obviate the need for ongoing breast surveillance.[17] In contrast, some maintain that mastectomy is unnecessary,[20] while others advocate localized radiation therapy as a primary method for managing the breast in OPBC patients.[18,19,21] Increased utilization of breast MRI, which has been estimated to identify a primary tumor in approximately 80% of mammogram-negative patients,[13] should elucidate the location of many previously

undetectable primary breast tumors and enable more patients to select breast conservation therapy.

In our series, four patients underwent mastectomy, including one patient whose clinically and mammographically OPBC was ultimately located on breast MRI and who, therefore, might have been a candidate for breast conservation therapy. But although it appears that breast MRI may help direct surgical management of clinically and mammographically OPBC, it has not been shown to decrease rates of local recurrence, increase the likelihood of negative surgical margins, or significantly prevent conversion from lumpectomy to mastectomy for non-occult tumors.[22] Furthermore, the relatively low specificity of MRI, which in contrast to mammography confers no radiation but does require injection of a contrast agent, means that many women will undergo additional procedures to follow up false-positive MRI findings.[22–26] Thus, while breast MRI is an important adjunct to mammography and ultrasound in OPBC management, its impact on patient care is not without cost.

Systemic therapy has historically been an important component of treatment for node-positive breast cancer, but its role in the management of OPBC may warrant additional investigation. A recent meta-analysis examining chemotherapeutic regimens for cancer of unknown primary (CUP) site, of which OPBC is a subset, found that no type of chemotherapy conferred a definitive survival benefit.[27] Furthermore, both endocrine and anti-HER2 targeted therapies – received by three and two members of our cohort, respectively – have provided less morbid alternatives to chemotherapy for many patients. All of the patients in our cohort received chemotherapy, and two suffered significant chemotherapy-related side effects. It may be that, in the future, chemotherapy will be limited to OPBC patients whose receptor statuses preclude use of endocrine and/or anti-HER2 therapy.

Personalized breast cancer treatment is increasingly sought by patients and, with ever greater effectiveness, being delivered by oncologists.[28] While OPBC has been presumed to have a similar natural history and biological profile (e.g., histology, receptor status) to non-occult node-positive breast cancers,[16,17] there is some evidence that it represents a more heterogeneous entity than previously thought. Pentheroudakis and colleagues have proposed that axillary nodal disease from CUP represents a different disease entity versus cases of CUP with visceral metastases that are biologically classified as breast cancer via microarrays, suggesting that the former is truly akin to node-positive, i.e., American Joint Commission on Cancer (AJCC) Stage II, breast cancer, while the latter may harbor additional genetic aberrations that cause it to behave differently and warrant different therapy.[17] But the variability in outcomes – excellent in most cases, very poor in others – among different series of OPBC patients presenting with axillary lymphadenopathy may indicate a gradient of acquired genetic aberrations that would merit treatment strategies tailored to a particular patient's biomarker and genetic profile; indeed a recent study demonstrated significantly different outcomes when comparing OPBC patients with different immunohistochemical profiles.[6] Thus the heterogeneity of treatment observed amongst OPBC patients both at our institution and in the medical literature[1–4,6,8–14,18–21,29–44] likely reflects appropriately tailored treatment for a given OPBC patient's profile. In our small cohort, the types of treatment received varied greatly, but all patients are alive with no evidence of disease several years after their initial diagnoses. Thus, although OPBC is an uncommon type of breast cancer, it may very well represent an opportunity to demonstrate the effectiveness of personalized breast cancer treatment. Furthermore, all breast cancer patients with atypical presentations are extensively discussed at our weekly, multidisciplinary tumor board. We believe that such discussions are

vital to the success of designing tailored approaches for patients with OPBC and other cases of breast cancer with complex presentations.

In conclusion, the results of our review support a curative-intent approach to treatment of this subset of locally advanced breast cancer patients and illustrate the need for individualized treatment algorithms based on tumor biology, patient preference, and extent of disease at diagnosis. Our patients had excellent outcomes, but they all received chemotherapy, which is associated with significant morbidity; future comparative-effectiveness studies are needed to determine if there is a survival difference between OPBC treatment courses that include or exclude chemotherapy. Furthermore, the extent to which OPBC warrants mastectomy is unclear. Finally, the role of breast MRI in management of OPBC will involve an ongoing assessment of the balance between the ultimate receipt of less morbid treatment potentially enabled by MRI's high sensitivity and the unnecessary procedures generated by its relatively low specificity.[22–26]

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Table 1

Characteristics of 7 Patients Diagnosed with Occult Primary Breast Cancer, 2002–2008 at Siteman Cancer Center, St. Louis, Missouri.

ID	Date of >Diagnosis	Age	Breast >MRI	Surgery	Chemotherapy	XRT	Targeted	LN Status[a]	Receptor Status	F/U (mos); >Status
1	2/21/02	65	9/16/02 (−)	9/25/02: R >MRM	3–9/02: ACx4	none	3–9/02: >Tamoxifen >10/02-10/07: >Tamoxifen	(−) post-adjuvant >chemotherapy	ER+/PR−[b]	114; ANED
2	6/5/02	72	6/20/02 (+) >11/7/02 (−)	11/19/02: R >Lx, ALND	7–10/02: ECx4 >12/02-2/03: >Tx4	3–5/03	none	N1	ER−/PR+/HER2−	124; ANED
3	7/11/02	42	7/23/02 (+)	11/26/02: R >MRM	8–11/02: >ACTHx4 >12/02-2/03: >ACx2	none	8–11/02: >Trastuzumab	N2	ER−/PR−/HER2−	81; ANED
4	8/6/03	65	8/11/03 (−)	11/24/03: L >ALND	9–11/03: ACx4	12/03-2/04	none	N1	ER−/PR−/HER2−[c] >ER−/PR−/HER2+[d]	34; recurrence[d] >112; ANED
5	9/24/04	40	10/7/04 (−)	1/20/05: L >MRM, R SM	11–12/04: ETx4 >2–3/05: ETx2	none	3/05-3/10: >Anastrozole	N1	ER+/PR+/HER2−	86; ANED
6	1/24/06	55	2/14/06 (−)	2/24/06: L >ALND	5–7/06: FECx4, >Tx3	8–9/06	3/06-5/07: >Trastuzumab	N1	ER−/PR−/HER2+	79; ANED
7	10/31/08	67	none	4/29/09: R >MRM	11/08-3/09: >TCx6	6–7/09	3/09-present: >Anastrozole	N1	ER+/PR−/HER2−	42; ANED

[a] Lymph node (LN) status prior to treatment except for one patient (as noted) whose LN status prior to adjuvant therapy was not recorded.

[b] HER2 status not tested

[c] Original tumor

[d] New contralateral, non-occult tumor detected 34 months after initial diagnosis with occult primary breast cancer (OPBC); treatments listed only refer to OPBC diagnosis

AC, doxorubicin/cyclophosphamide; ACTH, doxorubicin/cyclophosphamide followed by paclitaxel/trastuzumab; ALND, axillary lymph node dissection; ANED, alive with no evidence of disease; EC, epirubicin/cyclophosphamide; ER+, estrogen receptor positive; ER−,estrogen receptor negative; ET, epirubicin/taxane; FEC, 5-fluorouracil/epirubicin/cyclophosphamide; F/U, time to follow-up; HER2+, HER2/neu-amplified; HER2−, not HER2/neuamplified; L, center; Lx, lumpectomy; LN, lymph node; mos, months; MRI, magnetic resonance imaging; MRM, modified radical mastectomy; N1, 1–3 lymph nodes with malignancy; N2, 4–9 lymph nodes with malignancy; PR+, progesterone receptor positive; PR−, progesterone receptor negative; R, left; SM, simple mastectomy; T, taxane; TC, taxane/cyclophosphamide; XRT, radiation therapy