Casting-Type Calcifications With Invasion and High-Grade Ductal Carcinoma In Situ

A More Aggressive Disease?

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Hypothesis: Women with breast cancer who have casting-type microcalcifications associated with multifocal invasion and extensive ductal carcinoma in situ (DCIS) form a subset of patients with a poor prognosis. Our study aims to identify the mammographic and pathologic features of this group.

Design: Women with casting-type microcalcifications, multifocal invasion, and extensive DCIS were identified from our tumor board registry. Mammographic features, tumor characteristics, treatment, and survival rates were evaluated. Invasive tumors were limited to 14 mm or smaller.

Setting: University medical teaching hospital and breast cancer specialty clinic.

Results: Of the 984 patients with breast cancer treated at our center, 15 patients were identified who had extensive casting-type calcifications and DCIS. Twelve of these patients also had multifocal invasive breast cancer. All had casting-type microcalcifications occupying more than 1 breast quadrant. All but 1 of the patients were treated using mastectomy with sentinel node biopsy or axillary node dissection. All but 1 patient had extensive grade 3 DCIS. Invasive tumors were negative for estrogen receptor and progesterone receptor expression in half of the patients, and 60% were positive for the HER-2-neu receptor. Positive axillary lymph nodes were found in 33% of patients, and 75% received adjuvant chemotherapy. After a median follow-up period of 20.5 months (range, 6-72 months), 1 patient had died and 1 had distant metastases. Of the 3 patients who had DCIS without invasion, 1 experienced a recurrence with infiltrating ductal carcinoma.

Conclusions: In women with small multifocal breast cancers with extensive casting calcifications and DCIS, the incidence of positive lymph nodes was 33%, with a tendency for poor tumor markers. These women appear to be at substantial risk for systemic disease; lymph node sampling and adjuvant systemic therapy are recommended.

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With the increasing use of mammography, breast cancers are being recognized at smaller sizes and earlier stages. Overall, patients diagnosed as having breast cancers smaller than 1.0 cm have a low incidence of nodal metastasis and a relative 20-year survival rate in excess of 90%. However, a minority of patients with small breast cancers have an outcome similar to those with much larger cancers. Mammographic characteristics may be able to predict the outcome or pathologic aggressiveness of breast cancer. One mammographic criterion associated with malignancy is casting-type microcalcifications. Tabar et al observed that patients with small invasive cancers (1-14 mm) associated with casting-type mammographic microcalcifications had a 20-year survival rate of only 55%. In contrast, the 20-year survival rate for patients with cancers of a similar size and nodal status was 87%, and 95% for cancers smaller than 10 mm, when other patterns of microcalcification were present. The purpose of this study was to determine the outcome of patients with small breast cancers associated with casting-type microcalcifications.

Methods: Casting-type or branching-type microcalcifications have a distinctive mammographic pattern (Figure). Because our radiologic database does not code for Breast Imaging Reporting and Data System (BI-RADS) classification, abnormal mammograms were identified during the weekly tumor board presentations of the Breast Health Center (BHC), Providence, RI. All patients whose mammograms met the criteria for casting-type microcalcifications were selected. In addition, all patients with T1a and...
T1b tumors were evaluated to identify invasive cancers associated with casting-type microcalcifications. Our study cohort consisted of patients with invasive breast cancers smaller than 1.5 cm whose tumors were marked by casting-type microcalcifications. The mammograms of these patients were reviewed for accuracy.

The medical records for our study population were reviewed for pathologic reports, breast cancer treatment, and follow-up. Pathologic features recorded included size of the invasive cancer, number of invasive foci, presence and extent (reported as a percentage) of ductal carcinoma in situ (DCIS), grade, and expression of receptors for estrogen, progesterone, and HER-2-neu. Surgical treatment including whether axillary node dissection or sentinel node biopsy was performed as well as regional nodal status were recorded. Adjuvant radiotherapy and systemic treatment were noted. Patient status at the last recorded office visit was classified according to the following categories: alive with disease, alive with no evidence of disease, dead of disease, and dead of other causes without evidence of disease.

This study was evaluated and approved by the institutional review board of Women and Infants’ Hospital (Providence) and was conducted according to their guidelines.

RESULTS

During the 6-year study period (1995-2001), 984 patients underwent breast cancer treatment at our facility. Of this number, 15 patients were identified as having casting-type microcalcifications. This article describes the 12 patients who had a diagnosis of invasive breast cancer (Table). The remaining 3 patients had only DCIS; they are briefly discussed later in the article but are not part of our analysis. The median age of these 12 patients was 39 years (range, 31-56 years). All patients had multiple foci of invasive tumors; the median maximum diameter of the largest focus was 5 mm. The maximum size of any single focus of invasion was 14 mm, whereas the smallest invasive component consisted of multifocal invasion with each focus smaller than 1 mm. All tumors had an extensive intraductal component. The proportion of cancers that consisted of DCIS ranged from 85% to 99%, with a single exception (30%). The nuclear grade of the invasive in situ tumor was 3, with necrosis in 11 of the 12 patients; 1 patient had grade 2. Half of the tumors were negative for estrogen receptor and progesterone receptor expression; 60% were positive for HER-2-neu receptor amplification.

All patients but 1 had a total mastectomy because of the extentiveness of the calcifications and DCIS. One patient underwent a partial mastectomy followed by whole-breast radiotherapy. Axillary evaluation was initially carried out using sentinel node biopsy or axillary node dissection in 11 patients. Four patients had an initial axillary node dissection. Seven patients initially had a sentinel node biopsy, 1 of which revealed 2 node metastases; this patient then underwent axillary dissection, and no further positive nodes were found. No sentinel node could be identified in 1 patient, who received systemic chemotherapy. Four (33%) of 12 patients had nodal metastases; the median number of positive nodes was 6 (range, 2-9).

Patients with more than 3 nodal metastases received postmastectomy radiotherapy per BHC protocol. Nine (75%) of 12 patients received anthracycline-based adjuvant chemotherapy (doxorubicin and cyclophosphamide or cyclophosphamide, doxorubicin, and fluorouracil), 1 patient received cyclophosphamide, methotrexate, and fluorouracil, and 1 patient received tamoxifen citrate only; the remaining patient had no systemic therapy. Median follow-up time for all patients was 20.5 months (range, 6-72 months). One patient died of the disease 12 months after diagnosis, and a second patient had bone and visceral metastasis 27 months after diagnosis.

In addition to our study cohort, 3 patients with casting-type microcalcifications had DCIS only. No evidence of invasive disease was identified in these patients despite extensive sampling of the tissue. These patients all had mastectomies because of the extent of their disease. One of these patients experienced a recurrence in the reconstructed breast, with an invasive cancer and nodal metastasis (3 of 28 nodes were positive) 34 months after the initial diagnosis. She had no evidence of disease 4 years after completing neoadjuvant chemotherapy, surgical excision, axillary node dissection, and comprehensive nodal radiotherapy.

COMMENT

With the widespread application of mammographic screening, smaller breast cancers are being diagnosed. In patients with T1a and T1b (<10 mm) cancers, more than 90% remain free of disease for more than 10 years. Characteristics that have been reported as adverse prognostic factors include young age, presence of an extensive intraductal component, absence of hormone receptor expression in the primary tumor, high nuclear grade, presence of lymphovascular invasion, and HER-2-neu receptor overexpression.

The mammographic appearance of breast malignancies includes a stellate (spicular) or nodular lesion with or without microcalcifications, or microcalcifications only. Malignant microcalcifications generally have 1 of 3 appearances: crushed stone (pleomorphic), powdery, or casting-type. Mammograms with casting-type microcalcifications tend to be associated with a breast malignancy. Tabár et al postulated that this specific microcalcification pattern may be used to predict the his-
Demographic Information for Patients With Small Invasive Breast Cancers Associated With Casting-Type Microcalcifications

<table>
<thead>
<tr>
<th>Patient</th>
<th>Tumor Size, mm</th>
<th>Extent of DCIS, %</th>
<th>No. of Invasive Foci</th>
<th>ER/PR Receptor Expression</th>
<th>HER-2/neu Amplification</th>
<th>Positive Nodes</th>
<th>Surgery</th>
<th>Chemotherapy</th>
<th>Hormonal Therapy</th>
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<td>TM; SLNB</td>
<td>AC</td>
<td>NA</td>
<td>NED (23)</td>
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<td>7</td>
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<td>Negative/negative</td>
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<td>MRM</td>
<td>AC</td>
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<td>TM; SLNB</td>
<td>AC</td>
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<td>TM; SLNB</td>
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<td>Positive</td>
<td>8</td>
<td>MRM</td>
<td>AC</td>
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<td>AC</td>
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<td>NED (12)</td>
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<tr>
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<td>30</td>
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<td>AC, paclitaxel</td>
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<td>95</td>
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<td>Positive</td>
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<td>TM</td>
<td>AC</td>
<td>NA</td>
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<td>FAC</td>
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<td>AC</td>
<td>Tamoxifen citrate</td>
<td>NED (38)</td>
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</table>

Abbreviations: AC, doxorubicin and cyclophosphamide; ALND, axillary lymph node dissection; AWD, alive with disease; CMF, cyclophosphamide, methotrexate, and fluorouracil; DCIS, ductal carcinoma in situ; DOD, dead of disease; ER, estrogen receptor; FAC, fluorouracil, doxorubicin, and cyclophosphamide; MRM, modified radical mastectomy; NA, not applicable; NED, no evidence of disease; PR, progesterone receptor; SLNB, sentinel lymph node biopsy; TM, total mastectomy; WLE, wide local excision.

The adverse association between casting-type microcalcifications and high nuclear grade has previously been demonstrated for DCIS. Holland and Hendricks reported that linear and branching microcalcifications were associated with poorly differentiated DCIS. Hermann et al described 91 patients with linear or branching microcalcifications associated with comedo DCIS. However, not all studies supported a correlation between radiographic pattern and pathologic characteristics. Dinkel et al concluded that there was a poor mammographic-pathologic correlation and that the histologic characteristics of DCIS could not be predicted prospectively. However, their review did show that linear or branching microcalcifications tend to be associated with a higher pathologic grade.

When evaluated by size alone, these small invasive tumors are all within a range that should lead to a favorable prognosis. One of the most important prognostic factors after tumor size is axillary lymph node status. The rate of lymph node metastases for all T1 breast cancers ranges from 25% to 30%. Silverstein et al further defined the predictive value of lymph node metastases by primary cancer size. The rate of metastases to the axillary nodes for T1a, T1b, and T1c cancers was 3%, 17%, and 32%, respectively. One of our patients had a T1c cancer less than 14 mm in maximum diameter and had 9 positive nodes. Although the remaining 11 patients had tumors smaller than 10 mm (range, 1-9 mm), 3 had positive axillary nodes; the median number of positive nodes was 4, a far higher percentage than would be expected. The overall percentage of nodal metastasis for our study cohort was 33% (4 of 12). In addition to nodal metastasis, these cancers also had a tendency for poor prognostic features or markers: half were negative for estrogen or progesterone receptor expression, and 60% had overexpression of the HER-2-neu oncogene.

Young age is associated with a poor prognosis. The median age of patients with breast cancer in Rhode Island is 64 years (J. Fulton, written communication, August 15, 2002); for patients at the BHC, it is 50 years. The median age in our study cohort with invasive cancer was 39 years. Because of the young age, unfavorable prognostic markers, and the report by Tabár et al on poor prognosis associated with casting-type calcifications, anthra-
Cycline-based adjuvant chemotherapy was recommended to our patients regardless of node status; all but 2 received chemotherapy. One patient received tamoxifen alone, whereas the other had no systemic treatment. The patient receiving only tamoxifen had no nodal metastasis but developed bone and visceral metastases 27 months after the initial diagnosis. The 1 death from disease occurred in a patient in whom the largest focus was 5 mm and who had 8 metastatic nodes; she received adjuvant chemotherapy with doxorubicin and cyclophosphamide. Thus, 2 (17%) of 12 patients with small invasive breast cancers associated with casting-type microcalcifications will die of their disease after a very short follow-up period. This poor outcome with short follow-up (median, 20.5 months) far exceeds the 5-year mortality rate of 1% to 5% reported by the Surveillance, Epidemiology, and End Results database for node-negative tumors measuring 5 to 19 mm.11 Even if small and without nodal metastasis, invasive tumors accompanied by casting-type microcalcifications in addition to other poor prognostic features should be considered for aggressive systemic therapy. Even without areas of invasion, comedo-type DCIS with casting-type microcalcifications carries a high potential for recurrence, as recognized by high scores on the Van Nuys Prognostic Index reported by Silverstein et al.12

Our data support the hypothesis that small multifocal invasive cancers accompanied by extensive, high-grade comedo DCIS and associated with casting-type microcalcifications result in a poor prognosis. Women with breast cancer with this mammographic pattern are more likely to have adverse prognostic tumor markers, nodal metastases, and decreased survival rates compared with women who have tumors of similar size that lack these features.

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This study was presented at the 83rd Annual Meeting of the New England Surgical Society, Dixville Notch, NH, September 27, 2002, and is published after peer review and revision.

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REFERENCES


Correction

Incorrect Word. In the Invited Critique by Wilhelm and Prinz published in the February issue of the ARCHIVES (2003;138:151) the fourth sentence of the first paragraph should have read as follows: “The shift to radioiodine therapy has occurred because it is less expensive, less invasive, and relatively safe: avoiding the main surgical complications of hypoparathyroidism and recurrent laryngeal nerve injury.”