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Case Study

Nodal micrometastases in early stage breast cancer: two case reports

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Abstract The most important predictor of outcome for women with early stage breast cancer is the presence or absence of metastases in the axillary lymph nodes. In the era of sentinel lymph node biopsies and improved pathology techniques, micrometastatic disease can be diagnosed. The question of whether or not to treat these women as if they have nodal disease remains in doubt. In order to further explore this topic, we identified two cases of women with nodal micrometastases at our institution. A literature review of PUBMED and SABCS abstracts was then performed. In this article, we discuss our results and the emerging clinical debate about the management of nodal micrometastases.

Keywords: Micrometastases; Isolated tumor cells; Sentinel lymph node; Early stage breast cancer

Introduction

The single most important predictor of disease-free and overall survival in breast cancer is axillary lymph node status. Compared to approximately 30% of node-negative patients, as many as 70% of node-positive patients will develop recurrent disease within 10 years. In recent years, the importance of the findings of micrometastatic disease (areas of metastasis 0.2 mm to 2 mm in size) and even isolated tumor cells (less than 0.2 mm in size) has been questioned. Debate has continued as to whether these patients should be treated as if they are node-negative or node-positive. Recent data indicate that micrometastases may be prognostically significant [1,2], and that patients with occult micrometastases may have an improvement in disease-free survival (DFS) when treated with chemotherapy [2]. Here we discuss two examples of the treatment dilemma that arises in patients with nodal micrometastatic disease.

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Case report #1

Diagnosis and presentation

The patient is a 43-year-old premenopausal female, who was found to have a 0.9 cm infiltrating ductal carcinoma in her right breast in the region of calcifications seen on a routine mammogram. The tumor was estrogen and progesterone receptor positive, with H scores of 230 (60% of cells stained with 3+ intensity by immunohistochemistry and 25% with 2+ intensity) and 240 (80% of cells with 3+ intensity of stain), respectively. The tumor was her2/neu negative and had a Nottingham score of 5 out of 9. She underwent a right segmental mastectomy and sentinel node biopsy. Three sentinel nodes were identified, one of which showed evidence of micrometastatic disease, with a measurement of 1.8 mm. A full axillary lymph node dissection was

completed, and an additional 16 lymph nodes were found to be negative for disease. The patient underwent genetic counseling, and gene analysis failed to identify a *BRCA* gene mutation.

Treatment and outcome

The finding of micrometastatic disease was discussed with the patient. She was advised of the gap in medical knowledge about the relevance of this finding, and three potential options were given:

1. Treating her as if she had node-positive disease, with an anthracycline and taxane-based regimen;
2. Treating her with a 'node-negative' regimen, which would include taxotere and cyclophosphamide;
3. Sending her tumor for Oncotype DX testing to further assess potential risk of recurrence and benefit from chemotherapy.

The decision was made to send her tumor for Oncotype DX testing. Her recurrence score was 20, which equates to a 12% average rate of distant recurrence at 10 years with tamoxifen therapy alone. Based on these results, the patient opted for chemotherapy with taxotere and cyclophosphamide for four cycles followed by radiation therapy and tamoxifen. The patient tolerated the chemotherapy well and has now started on tamoxifen.

Case report #2

Diagnosis and presentation

The patient is a 61-year-old female, with a history of bipolar disorder with severe depressive episodes, seizures, and a cerebral aneurysm, who was found to have calcifications of the left breast on routine mammogram. She underwent a left-sided segmental mastectomy, which revealed two foci of infiltrating ductal carcinoma that were 4 mm and 2 mm in size. The tumors were estrogen and progesterone receptor positive, with H scores of 290 (90% of cells stained with 3+ intensity by immunohistochemistry and 10% with 2+ intensity) and 180 (60% of cells with 3+ intensity of stain), respectively. They were her2/neu negative with a Nottingham score of 6 out of 9. A sentinel node biopsy was done which revealed one of seven lymph nodes positive for micrometastatic disease with a maximal dimension of 2 mm. A complete axillary lymph node dissection followed which showed an additional nine lymph nodes that were negative for disease.

Treatment and outcome

The relevance of the finding of micrometastatic disease was discussed with this patient as well. In this case, her primary tumors were smaller and more strongly estrogen receptor positive. Her history of severe depression was quite concerning, as she had required electroconvulsive therapy in the past. The patient was more hesitant to undergo chemotherapy and was concerned about side effects. After discussion with the patient, we felt that the benefit of chemotherapy for her was likely to be outweighed by the potential side effects. We thus opted against chemotherapy and initiated radiation therapy along with an aromatase inhibitor. The patient is currently tolerating the aromatase inhibitor well with no evidence of disease.

Discussion

The introduction of sentinel lymph node (SLN) biopsy in the mid-1990s has led to a new dilemma in the management of nodal micrometastases. Prior to this era, the standard of care involved hematoxylin–eosin (H/E) staining and examination of just one or two sections of each lymph node obtained during a complete axillary dissection. The technique of SLN biopsy was adopted after it was shown that the SLN is the node that is most likely to be positive [3], and that a negative SLN is highly predictive that the remainder of the axillary lymph nodes will also be negative [4]. With this assurance, patients with a negative SLN can now avoid the morbidity associated with a complete axillary dissection [5,6].

The adoption of SLN biopsy increased the importance of correctly identifying involvement of the sentinel nodes. Pathologists began using serial sectioning and immunohistochemistry (IHC) to further scrutinize these lymph nodes for micrometastatic involvement [7]. These techniques have led to the identification of many patients with micrometastatic disease that would have previously been classified as node-negative. The importance of 'upstaging' these patients has been debated both in terms of treatment decisions and prognostic significance.

The clinical significance of nodal micrometastases remains controversial because some studies have shown that micrometastases do not affect prognosis [8,9] while others have indicated that they do [10,11]. These studies were all done retrospectively on axillary lymph node dissection specimens. In one such study, Kahn *et al.* [12] reevaluated axillary dissection specimens from a cohort of 214 patients that were found to be node-negative by standard techniques, between 1977 and 1986. Because 95% of the cohort did not receive chemotherapy, this was felt to be an accurate reflection of the natural history of micrometastases. After performing serial sectioning and IHC on these specimens, 29 of the 214 cases (14%) were found to have occult micrometastases. With an

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8-year follow-up, micrometastases did not appear to alter the disease-free interval ($P = 0.32$) or disease-specific survival ($P = 0.67$). The authors concluded that patients with micrometastatic disease have a similar prognosis to those without micrometastases.

In another recent study, however, occult micrometastases did have prognostic significance. Tan *et al.* [1] reevaluated axillary tissue specimens from 368 patients that were initially node-negative. By serial sectioning and IHC, 83 of 368 patients (23%) were found to be node-positive, which they defined as involvement of the node with any metastatic cells. They further subdivided nodal involvement by number of metastatic cells (0 cells, 1–20 cells, 21–100 cells, >100 cells) and then by the largest cluster size (⩽0.2 mm, 0.3–2.0 mm, >2.0 mm). On univariate analysis, 15-year DFS correlated significantly with both number of metastatic cells (81% for 0 cells vs. 50% for >100 cells; $P = <0.001$) and cluster size (81% for no cluster vs. 64% for ⩽0.2 mm, 41% for 0.3–2.0 mm, and 75% for >2.0 mm; $P = <0.001$).

More recent studies evaluating specimens obtained during sentinel node biopsy have continued to show mixed results. Chagpar *et al.* [13] reevaluated SLN specimens in 84 patients that were originally determined to be node-negative by conventional H/E staining. By serial sectioning and IHC, 15 patients (18%) were found to have occult micrometastasis. Of these 15 patients, five had received chemotherapy based on the characteristics of their primary tumor, but the remaining 10 did not. Although the sample size was small and the duration of follow-up was relatively short, they concluded that these patients had no difference in their disease-free or overall survival despite the difference in treatment.

The results of the MIRROR study were recently presented [2]. The investigators reviewed the Netherlands Cancer Registry to identify patients who were diagnosed with invasive cancer between 1997 and 2005. Patients were selected based on involvement of their sentinel node and then stratified as either pN0 (no nodal involvement), pN0(i+) (⩽0.2 mm as the largest cluster size), or pN1mi (>0.2 to 2 mm). Patients with primary tumors less than 1 cm in size or 1–3 cm that were of grade I-II were included. With these criteria, 2628 patients were identified: 828 patients with pN0 nodal status; 832 patients with micrometastatic disease who received no adjuvant chemotherapy; and 958 with micrometastases who did receive adjuvant chemotherapy.

The authors reported a 5-year DFS of 85.7% for patients with pN0 compared to 77.2% for patients with pN0(i+) ($P < 0.001$) and 76.4% for patients with pN1mi ($P = 0.003$) who did not receive adjuvant therapy. Patients with isolated tumor cells or micrometastases who did receive chemotherapy had a similar 5-year DFS to the pN0 patients (86.3%), indicating that chemotherapy eliminated the 9% reduction in 5-year DFS seen in untreated patients with micrometastases. While this data is preliminary, this is the largest study evaluating the prognostic significance of occult micrometastases in SLNs.

The studies evaluating the clinical significance of nodal micrometastatic disease have been conflicting. Many included relatively small numbers of patients, which limited the interpretation of results. Confounding factors include the varying definitions for nodal micrometastases, as well as the different pathologic techniques used in different studies. Additionally, the data from full axillary dissections can be difficult to interpret in an era of SLN biopsies. The decision of whether or not to treat micrometastases with adjuvant chemotherapy remains controversial, and prospective randomized studies are warranted to answer this important clinical dilemma.

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