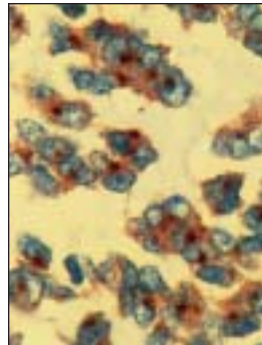


A CASE REPORT OF INVASIVE DUCTAL ADENOCARCINOMA IDENTIFIED IN A LYMPHATIC CHANNEL: A STAGING CONTROVERSY

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This feature presents special issues in oncologic pathology.

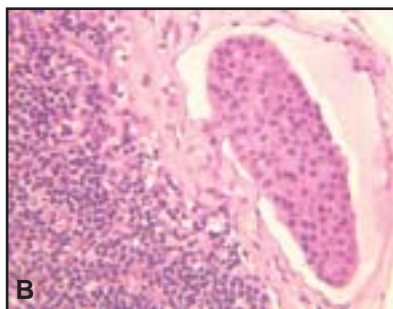
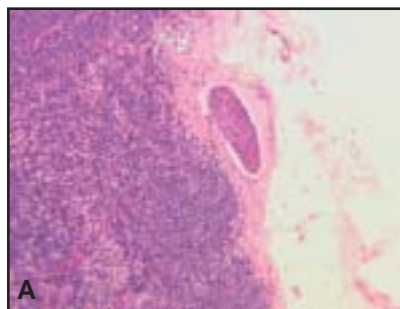
Case Report

A 65-year-old woman underwent core biopsy of a palpable left breast mass. This was a Nottingham grade II invasive ductal carcinoma with lymphovascular invasion. The tumor was ER/PR positive and Her-2/neu negative. The patient agreed to participate in the American College of Surgeon's Oncology Group Z00100 trial. Two weeks later, the patient underwent a left breast lumpectomy, sentinel lymph node (SLN) biopsy, and bone marrow biopsy. Lymphatic mapping and SLN biopsy were performed utilizing a combination mapping agent technique. Manual intermittent breast massage was performed for 5 minutes after injection of the mapping agents. A single SLN was identified that was both blue and "hot."

The SLN was 1.4 cm in size. The SLN was examined at three step-section levels, each 4 μm thick, separated by 40 to 80 μm and stained with hematoxylin-eosin (H&E). The primary breast carcinoma measured 3 cm in diameter and was Nottingham grade II (tubules 3, nuclear 2,

mitotic rate 1, total score 6). In addition to lymphatic invasion, circumferential perineural invasion was present. The SLN was negative for metastatic disease. However, a perinodal lymphatic channel was identified that contained metastatic infiltrating ductal adenocarcinoma (Figure). The metastatic tumor focus measured 0.1 \times 0.2 mm. As per the study protocol, no immunohistochemical (IHC) analysis was performed on the SLN. Both the size and the morphology of the tumor foci in the lymph channels invaded near the primary tumor were the same as that adjacent to the lymph node.

This case raises the question on how to appropriately stage the patient. We presume this lymphatic channel represents an afferent lymphatic draining from the breast tumor into the SLN. Unfortunately, this cannot be confirmed. Questions that should be asked include the following: Should this patient be considered N0? Should complete axillary lymph node dissection be recommended? Would this finding alter the decision on adjuvant cytotoxic chemotherapy? Would this finding alter treatment



Infiltrating ductal carcinoma in a lymphatic channel adjacent to the SLN at low power (A) and at high power (B).

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recommendations if the primary tumor had been less than 1 cm?

Lymphatic mapping and focused pathologic analysis of the SLNs have resulted in “upstaging” 10% to 20% of patients with breast cancer.^{1,5} The significance of this newly identified and previously unrecognized “occult” disease is a controversial topic, and the literature provides conflicting conclusions. Fortunately, well-designed prospective multi-institutional studies are underway to answer some of these questions.

The 6th edition of the American Joint Committee on Cancer (AJCC) staging manual⁶ and its TNM staging went into effect in January 2003. The revised staging system has reclassified axillary lymph node disease based on the size of the tumor and the method of identification (H&E, IHC, or molecular analysis). Micrometastatic disease is classified as lesions larger than 0.2 mm in diameter but no larger than 2.0 mm. These are staged as N1 regardless of the method of detection. H&E confirmation remains the gold standard though is not required for this designation — for example, pN1mi(i+) if detected only by IHC. A new classification, *isolated tumor cells*, has also been adopted. This recognizes metastatic foci less than 0.2 mm in the lymph node. These are classified as N0 regardless of the method of detection (H&E or IHC).

Isolated tumor cells are arbitrarily separated from micrometastases based on the size of the metastatic focus. The AJCC has

taken the position that it does not matter how tumor cells are identified (H&E or IHC), but the size of the metastasis is currently used as the determination for staging, as identified above. Micrometastatic disease represents implantation of tumor cells in the involved organ with extravasation, proliferation, and often a stromal reaction. It has been argued that this diagnosis can therefore be rendered only by histopathologic evaluation. Some pathologists also believe that they can determine which in-transit metastases are clinically significant in an individual patient, though this point remains controversial.

Epithelial cells have been demonstrated in the subcapsular sinus of draining lymph nodes after breast biopsy. This has been attributed by some to represent mechanical transport of tumor or normal breast epithelium and not cells with metastatic potential. Our SLN biopsy followed core breast biopsy and manual breast massage. The tumor cells in the lymphatic channel are thought to be located in the afferent lymphatics just proximal to entry into the subcapsular sinus.

It has been demonstrated that tumor cells, as well as benign ductal epithelial cells, can be transported to the lymphatic spaces and potentially to the lymph node by manipulation of the primary tumor.⁷ This manipulation includes breast biopsy and manual massage. The term *benign epithelial transport* has been coined for this phenomenon. The clinical significance of these cells is unknown at this point, but it is thought that these

tumor cells are shed into the interstitial spaces and forced into the lymphatic channels of the breast. The cells are carried through the lymphatics to the lymph node as passive passengers. Lymph flow is largely passive and can be influenced by tissue turgor and external compression. The pressure in the lymphatics is relatively low, but it has been demonstrated to increase 22-fold with external massage.⁸ Potentially, these isolated tumor cells are not true metastases and do not have malignant potential. They are present outside of the breast only because they were forced there and not because they acquired the ability to metastasize. If the SLN harboring these isolated tumor cells is removed immediately, the question of whether identifying these cells attains any prognostic value arises. As of now, the finding is noted by the pathologist, and the patient is staged as node negative — eg, pN0(i+).

These epithelial or cancer cells transport through the afferent lymphatic to the SLN. The tumor cells can flow directly to the pericapsular sinus and then successively to the central portion of the node. The lymph fluid then exits the lymph node through efferent lymphatic channels, thus potentially allowing tumor cells to be transported to the central circulation. Another less common pattern is for the cells to have direct communication to the hematogenous system through lymphaticovenous channels. These may exist in the pre-nodal sinus, allowing access to the circulation without traversing a lymph node.⁹ Lymph node metas-

tasis should also be associated with identifying lymphovascular invasion at the primary site, as in our report. However, this has not always been the case as this correlation has not been reported. In addition, this phenomenon, if it occurred frequently and was of clinical significance, would eventually cause a decrease in the survival of patients who had other nodal staging procedures. This does not seem to be the case, as patients staged to be node negative with the mapping procedure have a longer survival rate compared with historical patients staged to be node negative with complete axillary node dissection or even clinical examination.¹⁰ Lymphatic invasion and vascular invasion are important prognostic factors in individual series, but their significance is limited by poor reproducibility.¹¹

Our case is of interest for a number of reasons. Even if the theory that benign or malignant cells on occasion are transported as passive travelers to the lymph node is accepted, in our case it would not seem to apply. The tumor burden identified in the lymphatic channel appears too large to be a fragment of breast tissue that was transported into the breast interstitium and into the lymphatics by manual massage. As mentioned above, this phenomenon has been demonstrated to occur with isolated tumor cells but not with tumor emboli of 0.2 mm or greater in size. The tumor burden in the lymphatic channel met the AJCC size criteria of 0.2 mm to be classified as a metastasis and was identified by routine histologic evaluation as malignant.

However, the disease had not yet reached the lymph node itself. As a result of the study protocol, no IHC analysis was performed of the SLN. This was the only SLN involved with disease.

It is our opinion that this disease was identified in an afferent lymphatic and therefore no disease has reached the lymph node. The patient is thus classified as N0. The axilla is staged as negative and will be observed. The patient will be offered cytotoxic chemotherapy, then radiation to the ipsilateral breast, and then tamoxifen.

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