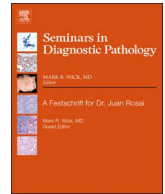




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Review article

Iatrogenically false positive sentinel lymph nodes in breast cancer: Methods of recognition and evaluation

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A B S T R A C T

With the introduction of sentinel lymph node (SLN) biopsy as a standard procedure for staging clinically node negative breast cancer patients, meticulous pathologic evaluation of SLNs by serial sections and/or immunohistochemistry for cytokeratins has become commonplace in order to detect small volume metastases (isolated tumor cells and micrometastases). This practice has also brought to the fore the concept of iatrogenically false positive sentinel nodes secondary to epithelial displacement produced largely by preoperative needling procedures. While this concept is well described in the clinical and pathologic literature, it is, in our experience, still under-recognized, with such lymph nodes frequently incorrectly diagnosed as harboring true metastases, possibly resulting in unwarranted further surgery and/or chemotherapy. This review discusses the concept of displaced epithelium in the histologic evaluation of breast surgical specimens and provides a stepwise approach to the correct identification of iatrogenically transported displaced epithelial cells in sentinel lymph nodes.

Introduction

The rigorous evaluation of sentinel lymph nodes for detecting small volume metastases [isolated tumor cells (ITCs) and micrometastases] in clinically node negative breast cancer patients is still a routine pathology practice even after the publication of results of recent clinical trials (ACOSOG Z10, NSABP B-32).^{1,2} Detailed and labor-intensive pathology protocols for sentinel lymph node processing (serial sections and immunohistochemistry for cytokeratins) undoubtedly have increased the detection of ITCs and micrometastases;^{2–7} however, this practice also has raised some concerns. For example, in our breast pathology consultation practice, we have often observed that iatrogenically displaced epithelial cells/clusters (DE) in the subcapsular sinuses of nodes are interpreted as ITCs or micrometastases by the original pathologist(s), sometimes altering patient management. Since sentinel lymph nodes are, by definition, the first lymph nodes in the lymphatic drainage pathway, the likelihood of finding displaced epithelial cells which have arrived via benign transport is highest in them. Incorrectly diagnosing these as metastatic carcinomas may result in upstaging, unwarranted complete axillary lymph node dissection, and/or chemotherapy. This paper reviews the concepts and features of dis-

placed epithelium in the histologic evaluation of breast surgical specimens, benign transport of epithelial cells, and resultant false positive sentinel lymph nodes and discusses the diagnostic approach for correct identification of DE.

Epithelial displacement in breast surgical specimens

Epithelial displacement secondary to preoperative needling procedures or surgical manipulation is a common diagnostic pitfall in the histologic evaluation of breast surgical specimens.^{8–14} Iatrogenically displaced fragments of benign or malignant ductal epithelium can remain entrapped in granulation tissue of the biopsy site and/or the biopsy tract and/or may enter in lymphatic channels and may subsequently spread to the draining sentinel node(s). This process is part of physiologic healing and has been termed “benign transport.”¹¹ As stated earlier, if not characterized appropriately, these findings can have significant unwarranted clinical implications.

Needling procedures are currently essential components of breast diagnostics and surgical practice and include core biopsy, fine needle aspiration, injection of dye for sentinel node detection, injection of local anesthetic, wire-localization either for initial diagnosis or for biopsy site

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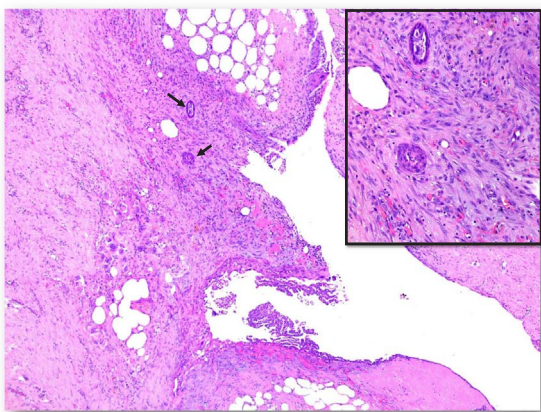


Fig. 1. Displaced epithelial fragments within the biopsy site granulation tissue (inset with higher magnification (X200) of DE highlighting the presence of myoepithelial cells). Note the associated papillary lesion.

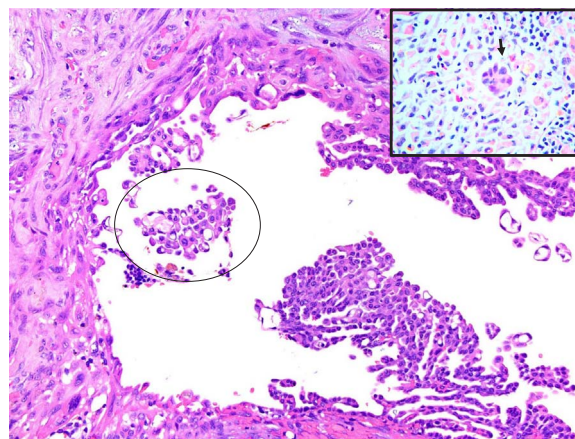


Fig. 3. Displaced epithelial fragments with micropapillary architecture (circle) seen in association with papillary DCIS. Inset shows the DE in the sentinel lymph node. Note the micropapillary architecture retained in the node.

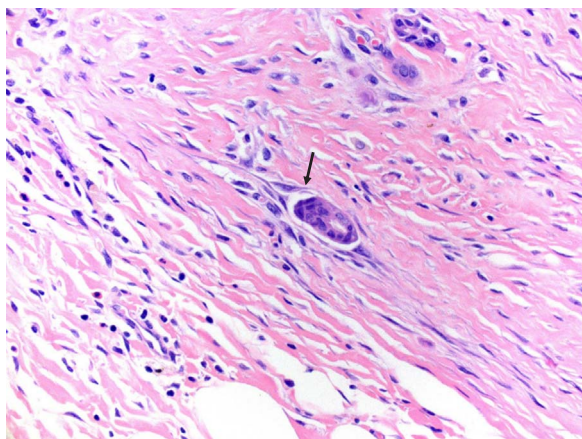


Fig. 2. Displaced epithelial fragment within the biopsy tract, associated with a retraction space (X200).

removal, and placement of sutures for surgical orientation of the specimen. In the 1990's, large gauge needle core biopsy replaced fine needle aspiration in most centers in the United States for the pre-operative diagnosis of palpable or nonpalpable image-detected breast lesions. The increasing use of core biopsy initially raised concerns over needle tract seeding by displaced tumor cells and its implications for tumor spread and recurrence.¹⁵⁻¹⁹ Almost concurrently, sentinel node biopsy for axillary staging in clinically node negative breast cancer patients was introduced and widely accepted across the country.²⁰⁻²² Fine needle aspiration and needle-localized excisions were routine even before the advent of needle core biopsy. Altogether, these needling procedures created some unforeseen challenges for pathologists in the histologic evaluation of breast excisional specimens. Youngson et al. in 1994 demonstrated the presence of epithelial displacement in the surgical breast specimens of 29 patients that underwent a needling procedure before surgery.⁸ In 26 cases, displaced epithelial fragments mimicking stromal invasion were present in breast fat or stroma

adjacent to or within the biopsy tract. Lymphatic epithelial emboli were observed in 7 cases, including 1 case with the additional finding of papillary epithelial clusters in the subcapsular sinuses of 2 axillary lymph nodes which were later dissected. Invasive carcinoma was identified elsewhere in the specimens only in 6 cases, including 2 cases with associated papillary intraductal carcinoma. In the remaining 23 cases with no evidence of an associated invasive carcinoma, the final diagnoses were as follows: papillary duct hyperplasia (3), usual ductal hyperplasia (1), intracystic papilloma (1), atypical duct hyperplasia (3), and intraductal carcinoma (15). Needle localization (13) was the most frequent pre-surgical procedure associated with epithelial displacement followed by FNA (8), local anesthesia injection (5), core biopsy (2), and suture placement (1). The authors concluded that epithelial displacement into breast stroma can occur due to traumatic disruption by needles or wires introduced before the surgery and should not be misinterpreted as true invasion by pathologists; however, the presence of epithelial clusters within the lymphatic channels or lymph nodes should be regarded as metastatic tumor until proven otherwise. In this study the authors could not comment on the frequency of epithelial displacement in breast specimens but in a later study (1995) of 43 consecutive cases with breast carcinoma in which stereotactic core biopsy was performed using a 14 G needle, the same authors reported a strikingly high incidence (28%; 12 out of 43 cases) of this phenomenon.⁹ In another study of 352 consecutive breast surgical excision specimens for carcinoma, Diaz and colleagues identified 114 cases (32%) with tumor displacement.²³ The overall incidence reported in the literature ranges from 7% to 36%.^{23,24}

Multiple factors individually or in combination can influence the rate of epithelial displacement.^{19,23,24} A high frequency of epithelial displacement in the context of papillary breast lesions was highlighted in one of our previous studies.²⁴ In this series of 53 cases with epithelial displacement, 50 (94%) had an associated papillary lesion, including benign intraductal papilloma, invasive papillary carcinoma, DCIS involving intraductal papilloma, and micropapillary and papillary types of DCIS. Cystic lesions and colloid carcinoma were also identified as predisposing factors. We conjectured that the inherent friability of papillary lesions renders them more easily prone to detachment and dislodgement by needling procedures and surgical manipulation. Likewise, cystic lesions, when punctured by a needle, can spill their contents and

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