Case Report

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Ductal Carcinoma *In Situ* Arising in Sentinel Axillary Lymph Nodes Excised From Patients With Breast Carcinoma - A Potential Diagnostic Pitfall. Report of Two Cases

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ABSTRACT

We present two cases of ductal carcinoma *in situ* (DCIS) that arose in axillary lymph nodes excised as the sentinel lymph node from two patients with breast carcinoma. The patient ages were 72 and 36 years and both patients underwent mastectomy and axillary lymph node dissection. In addition to DCIS in the sentinel lymph node, the first patient had a wide DCIS and microinvasion in the ipsilateral breast and a micrometastasis in another sentinel lymph node. The second patient was operated on after neoadjuvant chemotherapy and had DCIS and a small focus of invasion, in addition to invasive and *in situ* ductal carcinoma in the lymph node having signs of chemotherapy-induced regression. The presence of DCIS was confirmed by use of the immunohistochemical method with antibodies against myoepithelial cells. As a potential source of cellular origin, DCIS was accompanied by benign epithelial cell clusters in the lymph node in both cases. Morphologic and immunohistochemical features were similar in breast and lymph node neoplasms. We conclude that DCIS may rarely develop from benign epithelial inclusions in the axillary lymph node and is a potential diagnostic pitfall in cases having ipsilateral breast carcinoma.

Keywords: Breast; lymph node; ductal carcinoma *in situ*

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Key Points

- Ductal carcinoma *in situ* (DCIS) can develop from axillary lymph nodes.
- Pathologist should be aware of this rare situation to avoid misdiagnosis of metastasis because DCIS in the axillary lymph node is usually accompanied by ipsilateral breast carcinoma.

Introduction

The presence of benign epithelial inclusion (BEI) in the axillary lymph node is rare and its etiology is unclear (1-4). BEI in an axillary lymph node is often accompanied by ipsilateral benign or malignant breast diseases (4). Therefore, BEI in the axillary lymph nodes of patients with breast cancer can lead to false-positive diagnosis of metastatic disease (5). Similar to breast tissue, proliferative changes and atypia in epithelial cells have been reported in BEI in axillary lymph nodes (4). Ductal carcinoma *in situ* (DCIS) that developed within BEIs in an axillary lymph node has been reported in some cases where papillary lesions were present in the breast (6, 7). Furthermore, there are very few reports of DCIS that arose within BEIs in axillary lymph nodes that were not associated with the papillary lesions in the breast (8-10). The common feature of these cases is that only DCIS is detected in the breast.

Here we present two cases of DCIS encountered in a sentinel lymph node within BEIs occurring simultaneously with DCIS, microinvasive, and invasive carcinoma of the ipsilateral breast. We discuss the morphologic and immunohistochemical features, potential etiology and diagnostic significance.

Case Reports

Case 1: A 72-year-old female complained of a lump in her left breast. The lesion was palpable on physical examination. A digital mammogram showed an irregular, dense lump with pleomorphic calcifications. Sonographic examination confirmed the presence of irregular, hypoechoic tumor. An fluorodeoxyglucose (FDG)-positron emission tomography (PET) was also performed, which showed a left breast tumor maximum standardized uptake value (SUV_{max} 4.1) and minimal involvement in left axillary lymph nodes (SUV_{max} 1.4). A core biopsy of the breast lump was performed, and histopathological

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examination resulted in a diagnosis of high-grade DCIS with suspicion of microinvasion. On immunohistochemical examination, the neoplastic cells of the DCIS were negative for estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor-2 (HER-2), but positive for androgen receptor (AR).

The patient underwent a left mastectomy and sentinel lymph node (SLN) biopsy. An intraoperative pathologic examination using imprint cytology was performed in which two SLNs revealed metastasis, resulting in the completion of left axillary lymph node dissection. Grossly, the left mastectomy specimen contained an irregular tumor with firm to hard consistency and gray-white color, located in the upper lateral quadrant. The axillary dissection contained 13 grossly normal lymph nodes. The SLN biopsy specimen was composed of two lymph nodes, of which the largest one measured 1.2 cm, and they both partly stained with isosulphan blue dye. Both ER and PgR were negative in the DCIS and microinvasive carcinoma. One of SLNs contained a micrometastasis with two foci, of which the largest one measured 1.2 mm. Interestingly, the other SLN was extensively involved by a tumor displaying cribriform structures, reminiscent of the DCIS in the mastectomy specimen (Figure 1). Microscopic examination of the breast lump was reported as a high-grade DCIS with two foci of microinvasion, of which the largest measured 0.7 mm (Figure 2A, B). Additionally, an epithelial cell cluster, formed of squamoid cells, was observed beneath the capsule of the SLN. The cribriform structures in the SLN were formed of moderately atypical epithelial cells and contained an intact myoepithelial cell layer, which was evident even during examination of the slides stained with standard hematoxylin-eosin (Figure 2C, D). The presence of myoepithelial cells at the periphery of the cribriform structures of the SLN was confirmed with positive immunostaining with p63 (Figure 2E) and cytokeratin 14 (Figure 2F). Serial sectioning showed no sign of invasion in this SLN, and a diagnosis of DCIS arising in the lymph node was established. The neoplastic cells were negative for ER and PgR and positive for AR, similar to the DCIS from the left breast. The rest of the lymph nodes in the axillary dissection were free of tumor.

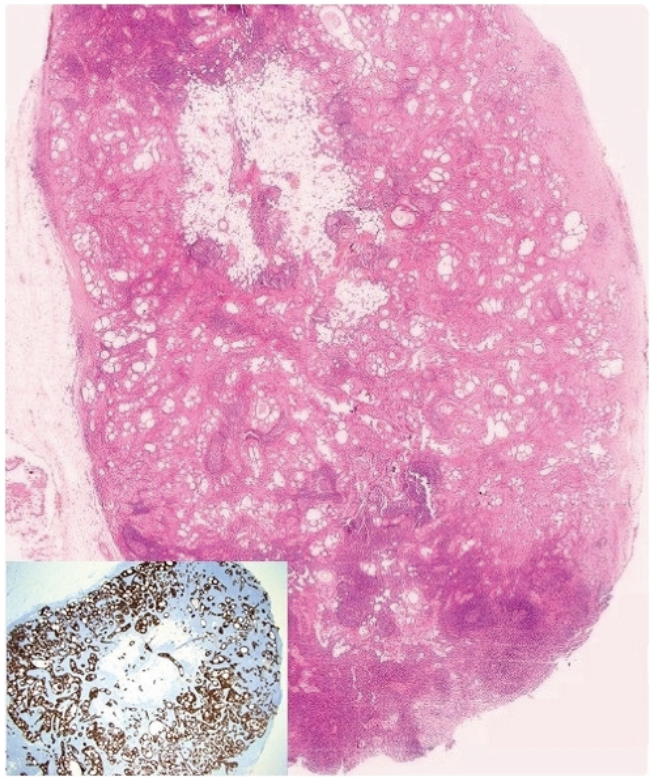

Figure 1. Extensive *in situ* ductal carcinoma in sentinel lymph node, and immunostaining by pancytokeratin (inset), (hematoxylin-eosin, x2; pancytokeratin, x40) (inset)

Case 2: A 36-year-old female suffered from a lump in her right breast and nipple discharge. A sonographic examination showed an irregular, hypoechoic mass with microcalcifications that measured 33 mm. Magnetic resonance imaging analysis showed heterogeneously contrasted right breast lesion that measured 47 mm. A F-18-PET (FDG-PET) analysis also revealed a tumor in the right breast (SUV_{max} 9.0), that measured 37 mm and right axillary lymphadenomegaly (LAM) (SUV_{max} 3.1) measuring 15 mm. Fine needle aspiration from the LAM was not diagnostic, but microscopic examination of a core biopsy of the right breast lump established a diagnosis of invasive carcinoma of no specific type. An immunohistochemical examination revealed that the neoplastic cells were positive for ER and PgR and negative for HER-2, and the Ki-67 proliferation rate was 15%. Following neoadjuvant chemotherapy (Doxorubicin/Cyclophosphamide, Paclytaxel), the patient underwent a right mastectomy and right axillary dissection after an intraoperative histopathological diagnosis of metastasis in the right axillary SLN.

During gross examination of the mastectomy specimen, a mass of 2.5 cm with firm to hard consistency and yellowish-gray colour was observed. The SLN biopsy specimen contained two lymph nodes, the largest of which measured 1.6 cm. The axillary dissection specimen contained 16 lymph nodes. Microscopic examination of the breast lesion revealed a 2.5 cm DCIS and a 1.5 mm invasive carcinoma.

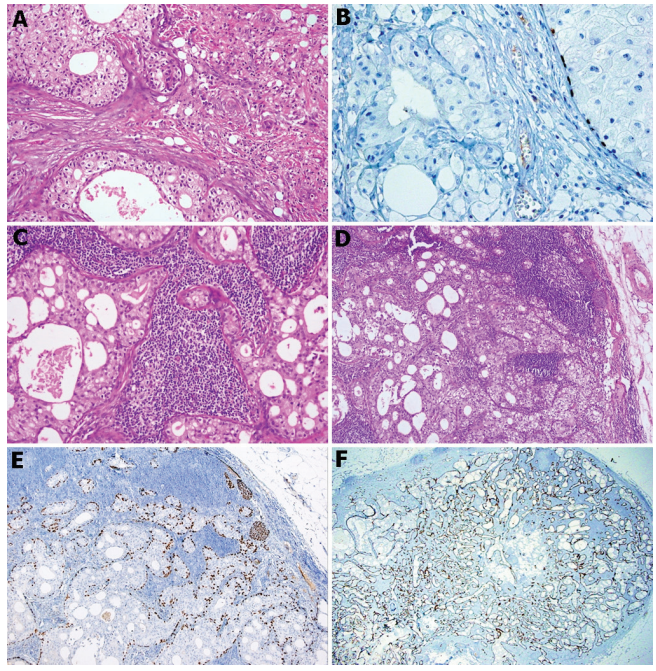

Figure 2A. High grade ductal carcinoma *in situ* with microinvasion in the breast, **B.** Ductal carcinoma *in situ* with immunoreactivity for p63, **C.** Ductal carcinoma *in situ* in the sentinel lymph node, **D.** Squamous inclusions and ductal carcinoma *in situ* in the sentinel lymph node, **E.** Immunohistochemistry for p63 shows a myoepithelial layer around the islands of epithelial cells, and squamous inclusions, **F.** Ductal carcinoma *in situ* with immunoreactivity for cytokeratin 14 (A: hematoxylin-eosin, x200; B: p63, x400; C: hematoxylin-eosin, x200; D: hematoxylin-eosin, x100; E: p63, x100; F: cytokeratin 14, x40)

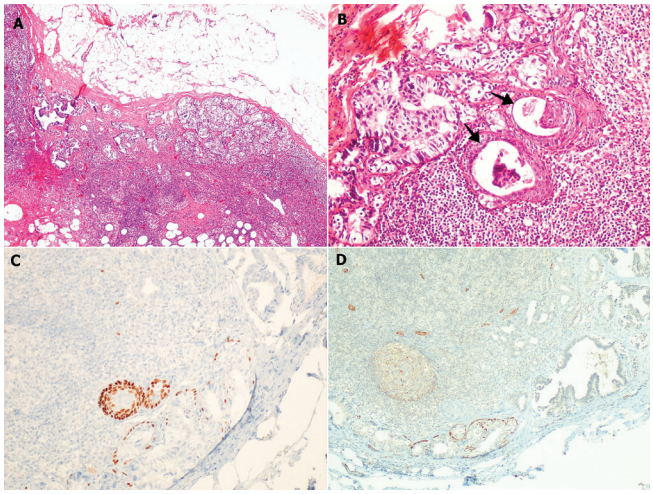

Figure 3A. Infiltrative metastatic carcinoma, and ductal carcinoma *in situ* in the sentinel lymph node, **B.** Ductal carcinoma *in situ*, and benign epithelial inclusion of skin adnexa-type (acrosyringeal) (arrows), **C.** Ductal carcinoma *in situ* and inclusions with immunoreactivity for p63, **D.** Ductal carcinoma *in situ* with immunoreactivity for smooth muscle myosin (A: hematoxylin-eosin, x100; B: hematoxylin-eosin, x200; C: p63, x200; D: smooth muscle myosin, x200)

Although the entire lesion was sampled, broad areas of fibrosis, suggestive of regression due to neoadjuvant chemotherapy were not detected, but only scattered foci within the DCIS-involved breast tissue. One of the SLNs contained metastatic carcinoma. However, on detailed microscopic examination, a microscopic focus of DCIS within the SLN, in addition to infiltrative metastatic carcinoma, and a microscopic focus of BEI of skin adnexa-type, and an area of fibrosis suggestive of tumor regression due to neoadjuvant chemotherapy (Figure 3A, B) were reported. The DCIS within the SLN was formed by cribriform structures containing an intact myoepithelial cell layer that stained positive for p63 (Figure 3C), smooth muscle myosin (SMM) (Figure 3D), and cytokeratin 14 on immunohistochemical examination. The neoplastic cells of the DCIS and infiltrative carcinoma within the SLN were similar in terms of nuclear size and atypia. The rest of the lymph nodes were free of metastasis.

Discussion and Conclusion

BEIs can occur in many anatomic sites, such as axilla, pelvis, and mediastinum (4, 11, 12). In axillary lymph nodes, BEIs include glandular inclusions (mammary-type and Mullerian-type), squamous inclusions, and mixed glandular-squamous inclusions (4). Since BEIs are associated with various breast diseases, they can pose a potential diagnostic pitfall in cases of metastatic carcinoma.

BEIs in the axillary lymph node may exhibit proliferative changes similar to breast tissue (6, 13). Furthermore, neoplastic change/alteration is also possible. In the literature, few cases of BEI-related DCIS in the axillary lymph nodes have been reported, accompanied by papillary lesions in lymph node and breast (6, 7). Additionally, there have been three reported cases of DCIS involving non-papillary BEI in the axillary lymph nodes (8-10). In all of these cases, only DCIS was detected in the breast tissue. In the two cases presented, there was BEI-related DCIS that was not accompanied by a papillary lesion. In contrast to previous reports, the presented cases demonstrated invasive carcinoma of the breast, as well as diffuse DCIS.

The presence of BEIs in axillary lymph nodes is often associated with implantation/displacement, metaplasia, or embryonic rests (7). In some studies, mechanical transport has been described as an alternative reason for the presence of epithelial cells in axillary lymph nodes (14, 15). It is known that mechanical transport is usually detected in papillary lesions and in the cases where a history of surgical manipulation of breast lesion has occurred (15). Morphologically, it presents as epithelial cells located in the subcapsular sinus, accompanied by erythrocytes and hemosiderin-laden macrophages (14). However, this etiologic reason does not explain well-organized BEIs nor DCIS in lymph node (6, 15).

It is assumed that DCIS develops in a BEI due to the presence of a separate benign glandular structure within the same lymph node (8). In the gynecological system, involvement of pelvic lymph node by a borderline tumor of ovarian type is also explained by the exposure of the ovary and lymph nodes to the same carcinogenic effects (16). The etiology of DCIS development from epithelial cells in the axillary lymph node is unclear. Nevertheless, we suggest that these cells in the lymph node have been exposed to the same carcinogenic effect as epithelial cells in the breast (8, 9). In support of this hypothesis, in a few reported cases, DCIS morphology in both lymph node and breast has been shown to be similar (8-10). Srinivasan et al. (8) and Commander et al. (10) demonstrated similar positivity for ER in the DCIS in both breast and the lymph node. We also detected similar morphologic and immunohistochemical features in the DCIS in both the breast lesion and the lymph node in one of the cases.

In contrast to earlier cases with small foci of DCIS in the axillary lymph node, a striking feature in one of the presented cases was that the lymph node that measured 1.2 cm was entirely involved by DCIS. Although it may be supposed that there is a ductus system in the lymph node, as in the breast tissue, there is no theoretical development of the ductus system in the lymph node. However, ductus-like structures filled with neoplastic cells, and development of stroma have been described and defined as "neoductgenesis" in breast tissue (17). It has been reported that this structuring is associated with cases of widespread neoplasia (18). The widespread involvement of lymph node by DCIS in our case, may be explained with this "neoductgenesis" theory.

Retrograde differentiation refers to the phenomenon where cancer cells that have already metastasized can revert to a less aggressive state. The hypothesis suggests that these cells may form structures like the myoepithelial layer. However, the literature lacks sufficient data on this subject. It is important to note that further research is required to gain a better understanding of retrograde differentiation and other potential mechanisms.

While BEIs are potential diagnostic pitfall areas, the presence of atypia and proliferative changes in epithelial cells makes the situation more complicated. Misinterpretation of the presence of DCIS in the lymph node could significantly affect clinical management. Indeed, BEI-related DCIS detected in the lymph node does not mean metastasis. Moreover, histopathologists dealing with breast carcinoma cases are aware that true metastases, morphologically mimicking DCIS, are common in axillary lymph nodes (19). To differentiate DCIS from true metastasis, it is helpful to perform immunohistochemical investigations to identify the myoepithelial cells, as is usually done in breast neoplasms. DCIS may be overlooked when there is a large invasive tumor area in the lymph node. As in our case, if the patient has received neoadjuvant chemotherapy treatment, the chance of DCIS being found in the lymph node increases. In other words, regression of the invasive tumor with chemotherapy makes the DCIS evident.

In conclusion, DCIS can develop in axillary lymph nodes. Pathologist should be aware of this rare situation to avoid misdiagnosis of metastasis because DCIS in the axillary lymph node is usually accompanied by ipsilateral breast carcinoma.

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Surgical and Medical Practices: M.T.; Concept: S.Ö., E.Y.; Design: A.B., S.Ö., E.Y.; Data Collection and/or Processing: A.B.; Analysis or Interpretation: A.B., S.Ö., E.Y.; Literature Search: A.Y.A., S.B.; Writing: A.B.

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