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Sentinel Lymph Node Involvement by Epithelial Inclusions Mimicking Metastatic Carcinoma: A Diagnostic Pitfall

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Female, 70-year-old
Final Diagnosis: Epithelial inclusion cysts
Symptoms: Abnormal mammogram findings
Medication: —
Clinical Procedure: —
Specialty: Pathology

Objective: Rare disease
Background:

An epithelial inclusion cyst within a lymph node denotes a heterotopic phenomenon. Nodal epithelial inclusion cysts have been reported in a variety of anatomical locations including pelvic, abdominal, mediastinal, and axillary regions. While nodal melanocytic nevus (also known as nevus cell aggregates) is the most common heterotopic phenomena involving the axillary lymph nodes, the presence of benign epithelial inclusion cysts in axillary lymph nodes is a rare but well-reported finding. Such documentation is in part due to assessment of sentinel lymph nodes in breast cancer becoming standard of care. These epithelial inclusion cysts offer a diagnostic pitfall in evaluation of sentinel lymph node in the setting of breast carcinoma. They also complicate assessment of sentinel lymph node during intraoperative frozen sections analysis.

Case Report: We report a case of co-existent of benign squamous-type and glandular-type epithelial inclusions cysts in 2 sentinel lymph nodes in a patient with grade III invasive ductal carcinoma involving the left breast. There have been at least 4 cases reported in literature in which benign epithelial inclusion cysts in sentinel lymph nodes were first mistakenly diagnosed as metastatic carcinoma both during intraoperative frozen section analysis and during review of permanent sections. The missed diagnosis could potentially occur intraoperatively during frozen section sentinel lymph node analysis secondarily due to lack of availability of the primary tumor for comparison and inability to use immunohistochemical stains.

Conclusions: Pathologists should be aware of this pitfall especially in frozen section analysis of sentinel lymph node to avoid misdiagnosis and its associated potential grave consequences.

MeSH Keywords: Breast Neoplasms • Frozen Sections • Lymph Nodes • Sentinel Lymph Node Biopsy

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/926094>



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Background

Although rare, benign epithelial inclusions involving the axillary lymph nodes offer a diagnostic pitfall in evaluation of sentinel lymph node in the setting of breast carcinoma. It provides a further complication to assess sentinel lymph node during intraoperative frozen sections analysis. There are only a few reported cases in which benign epithelial inclusion cysts have been misdiagnosed as metastatic carcinoma.

We report a case of co-existent of benign squamous-type and glandular-type epithelial inclusions in 2 sentinel lymph nodes.

Case Report

A 70-year-old woman presented for follow-up mammography. She had a medical history of right-breast invasive ductal carcinoma 10 years ago, status post right modified radical mastectomy. Her previous left-breast mammograms, last performed 2 years ago, were negative of any concerning features.

The latest mammogram demonstrated heterogeneously dense fibroglandular tissue present in the left breast with development of extensive regional amorphous calcifications throughout the upper outer quadrant. Also noted was a new asymmetric density located in the upper outer quadrant with prominent pleomorphic calcifications. Axillary adenopathy was not identified.

A subsequent left-breast MRI revealed widespread clumped enhancement throughout much of the left breast, particularly in the central and lateral thirds. No suspicious lymph nodes were identified in the left axilla. The patient underwent biopsy of the left breast, which yielded a diagnosis of grade III invasive ductal carcinoma.

The patient consequently had left total mastectomy and sentinel lymph nodes sampling. Gross examination of the sentinel lymph nodes demonstrated multiple cysts filled with yellow material and measuring up to 1 cm in greatest dimension (Figure 1) involving 2 lymph nodes. The third sentinel lymph node was grossly unremarkable.

The mastectomy specimen had multiple foci of grade III invasive ductal carcinoma (Figure 2) with the largest invasive foci being 1.2 cm (T classification: pT1c). Ancillary studies performed demonstrated the carcinoma was ER-positive, PgR-positive, and HER2-negative. Based on these findings, including pN0 lymph node status, the patient's AJCC stage was IA. Histologic examination of the sentinel lymph nodes demonstrated co-existence of both squamous-type and glandular-type epithelial inclusions. The squamous-type epithelial inclusions formed cystic structures, which were lined by squamous



Figure 1. Two sentinel lymph nodes demonstrating multiple cysts filled with yellow “caseous” material.

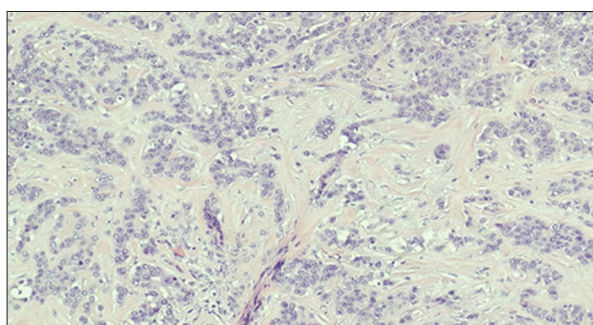


Figure 2. Section of mastectomy specimen demonstrating grade III invasive ductal carcinoma.

epithelium and filled with keratin debris (Figure 3). The glandular-type epithelial inclusions presented as either small ducts or large round tubular- or papillary-shaped glandular structures. On high magnification, the epithelial cells had a Müllerian appearance with microvilli and apical eosinophilic cytoplasmic snouts (Figure 4). No desmoplastic reaction was identified around the inclusions and no cytologic atypia or mitosis were noted at the epithelial cells. A thin layer of collagen fiber and myoepithelial cells were identified around the inclusions, and P63 immunostains confirmed the presence of myoepithelial cells (Figure 5).

Discussion

Nodal epithelial inclusion cysts have been reported in a variety of anatomical locations, including pelvic, abdominal, mediastinal, and axillary regions [1–5]. Involvement of axillary lymph nodes is a rare but well-reported finding [6]. Such documentation is in part due to assessment of sentinel lymph nodes in breast cancer becoming the standard of care. Histologically, there are 3 types of epithelial inclusion cyst: glandular-type inclusions, squamous-type inclusions, and mixed glandular-squamous-type inclusions [5,7].

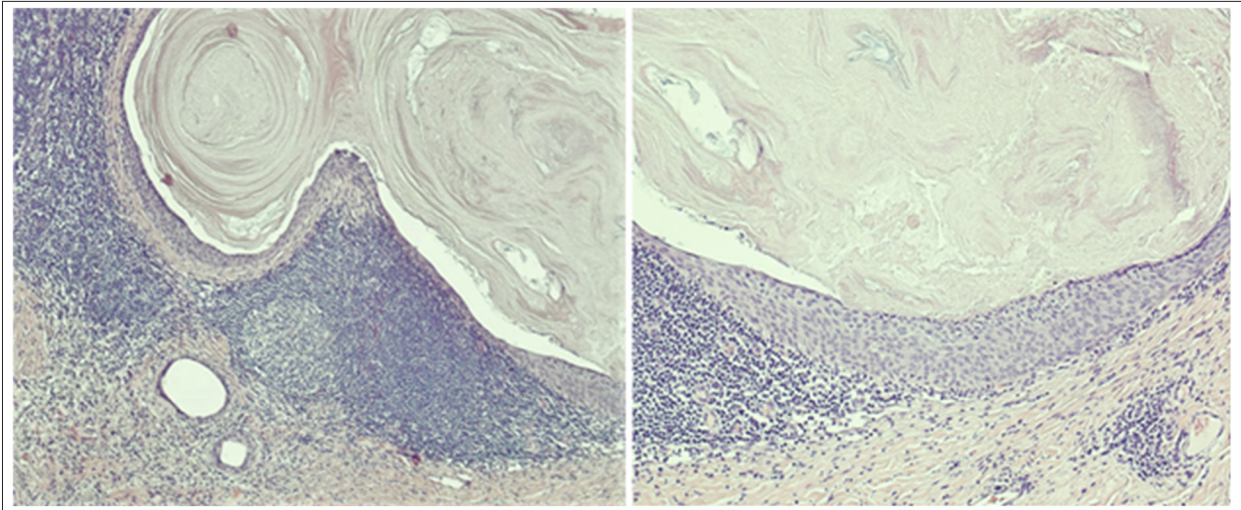


Figure 3. Nodal squamous-type inclusion cyst lined by stratified squamous epithelium and filled with abundant keratin debris.

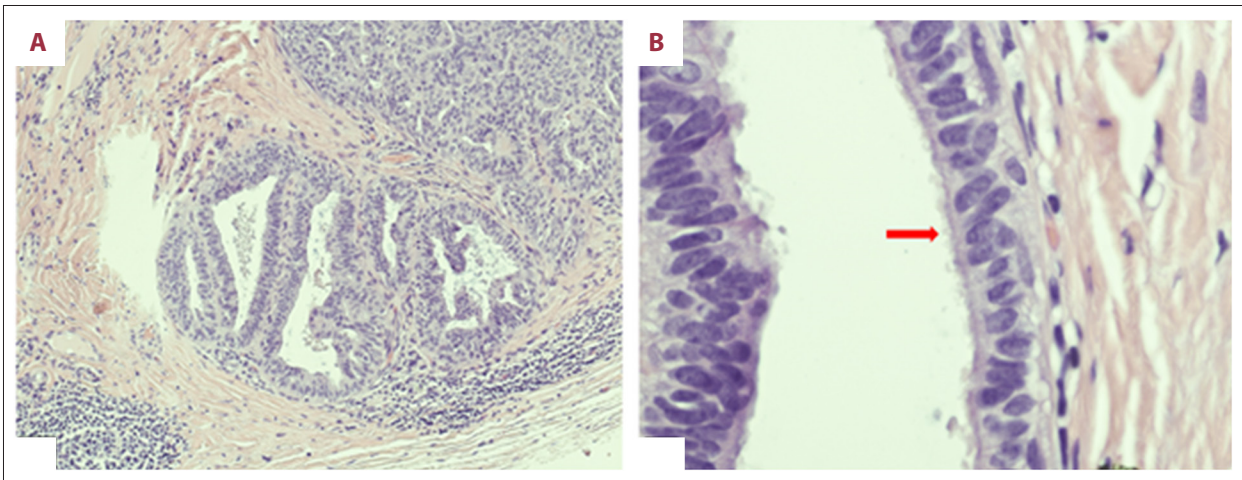


Figure 4. The glandular-type epithelial inclusions with large round tubular and papillary-shaped glandular structures (A). On high magnification, the epithelial cells have a Müllerian appearance with microvilli (arrow) (B).

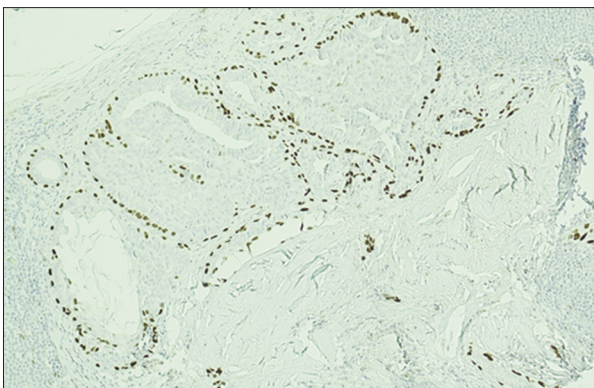


Figure 5. P63 immunostains highlighting myoepithelial cells present in the glandular-type epithelial inclusion cyst.

Among the 3 types, the glandular-type inclusions are the most common. They are typically located within the capsule or sub-capsular space. Although they are histomorphologically heterogeneous, their characterizing feature is the presence of round, tubular-shaped, glandular structures that can be further characterized into “breast-like” or “Müllerian-like” cysts. The glandular-type breast-like inclusion cysts have tissue architecture resembling benign or malignant breast tissue. The glandular-type Müllerian-like epithelial inclusion cysts typically have columnar epithelium with microvilli.

In contrast to glandular-type inclusion cysts, squamous-type inclusion cysts seem to be rarer and are typically located within the intraparenchymal space of the lymph node rather than in the capsular area. Grossly, as described in our case report, the squamous-type inclusion cysts contain yellow-green “caseous” material. Histologically, they are lined by stratified

squamous epithelium and filled with abundant keratin debris. The third type of cysts, mixed glandular-squamous-type inclusions, have characteristics similar to both glandular-type and squamous-type cysts.

In the literature, different authors have postulated possible origins of nodal epithelial inclusion cysts. The “benign metastasis” theory suggests the lesions occur as a result of embolization of breast tissue following manipulative processes such as breast examination, needle-core biopsy, or surgery [8]. In patients with no history of breast manipulation, other suggested theories include metaplasia of pluripotent cells and embryological maldevelopment resulting in nodal epithelial crests [9].

Cases of benign epithelial inclusions in axillary lymph nodes have been reported in women both with and without a history of breast pathology [7]. In the largest combined study to date, out of the 18 cases reviewed, 13 cases (72%) had a previous diagnosis involving the breast, 9 of which were invasive breast malignancies. Also noted is that epithelial inclusions were identified in sentinel lymph nodes in 9 (50%) of the 18 cases.

Rarely, the epithelial inclusion cysts are found in lymph nodes concomitantly with metastatic breast carcinoma. A report by Fisher et al. describes a case in which a 55-year-old woman with an infiltrating ductal carcinoma had 2 lymph nodes removed during axillary dissection that were positive for both metastatic carcinoma and epithelial inclusion cysts [10]. The presence of epithelial inclusion cysts in sentinel lymph nodes presents a diagnostic pitfall. There have been at least 4 cases reported in the literature in which benign epithelial inclusion cysts in sentinel lymph nodes were first mistakenly diagnosed as metastatic carcinoma [11,12]. False-positive sentinel lymph node diagnoses often lead to unnecessary complete axillary node dissections [11], exposing the patient to possible complications such as lymphedema, pain, paresthesia, and restricted physical activity [13].

The missed diagnosis often occurs intraoperatively during frozen section sentinel lymph node analysis. This can be attributed to lack of availability of the primary tumor for comparison [12], especially since glandular-type inclusions can mimic macrometastases. In addition, immunohistochemical stains cannot be utilized during frozen section analysis and the basement membrane myoepithelial cell layer may be difficult to differentiate. It is due to this ambiguity that a safer approach is recommended. Further surgery should be delayed if a positive diagnosis cannot be differentiated with certainty.

Despite the above challenges, certain characteristics may help to distinguish an epithelial inclusion cyst from metastatic carcinoma during assessment of sentinel lymph nodes. Benign cysts are more commonly located in the fibrous portion of the lymph node, while metastatic disease is more likely to be detected within the parenchyma [12]. The cells of epithelial inclusion cysts are frequently architecturally orderly arranged [1] and lack cytological atypia [14]. Due diligence should be taken in case of a ruptured cyst where reactive changes in addition to inflammatory response are present. Lastly, the presence of a basement membrane and myoepithelial cell layer should be identified if possible [14].

To prevent this diagnostic pitfall, strategies that can be utilized include differing uncertain frozen section diagnosis to permanent section analysis, use of immunohistochemical stains, and comparison of primary tumor morphology with the lesion in a sentinel lymph node.

Conclusions

We report a case of axillary sentinel lymph node involvement by both squamous-type and glandular-type epithelial inclusions, mimicking metastatic breast carcinoma. The presence of epithelial inclusion cysts in sentinel lymph nodes presents a diagnostic pitfall with potentially grave consequences. Pathologists should be aware of this pitfall, especially in frozen section analysis of sentinel lymph nodes to avoid any misdiagnosis.

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