Axillary Lymph Node Inclusions

Ashley Cimino-Mathews, MD

KEYWORDS

• Axillary lymph node • Lymph node inclusions • Endosalpingiosis • Nodal nevi

Key points

- Lymph node inclusions include both epithelial inclusions and nonepithelial inclusions.
- Epithelial lymph node inclusions include mammary-type glandular inclusions, Mullerian-type glandular inclusions, squamous inclusions, and mixed glandular-squamous inclusions.
- The primary diagnostic pitfall with glandular lymph node inclusions is metastatic mammary carcinoma, or metastatic adenocarcinoma of another site, such as the gynecologic tract.
- Nonepithelial inclusions include nodal nevi, and the primary diagnostic pitfall with nodal nevi is metastatic melanoma or less commonly metastatic spindle cell (sarcomatoid) mammary carcinoma.
- Examining the histologic features of the nodal inclusions, comparing the inclusion with the primary mammary carcinoma, and performing a targeted immunohistochemical panel can resolve the diagnosis.

ABSTRACT

Lymph node inclusions can occur in axillary lymph nodes, where they can mimic metastatic breast carcinoma. This article provides an overview of epithelial and nonepithelial lymph node inclusions, including mammary-type glandular inclusions, Mullerian-type glandular inclusions, squamous inclusions, mixed glandular-squamous inclusions, and nodal nevi. The discussion emphasizes the histologic and immunophenotypic features and differential diagnoses of each entity.

OVERVIEW

Benign lymph node inclusions can occur in any anatomic location, including the axilla, where they pose a potential diagnostic pitfall in the evaluation of sentinel lymph nodes in patients with breast carcinoma. Lymph node inclusions fall into 2 broad categories: epithelial, and nonepithelial (**Box 1**).[1] Epithelial inclusions include those that consist of mammary-type glandular epithelium, Mullerian-type glandular epithelium, squamous epithelium, and mixed glandular-squamous epithelium. Nonepithelial inclusions include benign nodal nevi.

The potential for misdiagnosis of a benign lymph node inclusion as metastatic breast carcinoma is greatest on frozen section evaluation of sentinel lymph nodes,[2] where frozen section artifact can obscure cytologic detail, sections of the primary tumor are often not available for histologic comparison, and the intraoperative nature generally precludes the use of supplemental immunohistochemistry. Fortunately, in this regard, the frequency of frozen section analysis of sentinel lymph nodes has in general decreased with the results of the ACOSOG Z0011 trial indicating that axillary radiation can supplant surgical axillary nodal dissection for a subset of patients with axillary nodal disease.[3,4] However, diagnostic pitfalls of nodal inclusions still remain in permanent histologic sections of lymph node evaluation (**Box 2**, **Table 1**).[2,5,6]

Disclosure Statement: The author declares no financial disclosures or conflicts of interest.
Department of Pathology, Johns Hopkins Hospital, 401 North Broadway Street, Weinberg 2242, Baltimore, MD 21287, USA
E-mail address: acimino1@jhmi.edu

Surgical Pathology ■ (2017) ■–■
https://doi.org/10.1016/j.path.2017.09.004

Box 1
Pathologic Key Features of Nodal Inclusions

1. Mammary-type glandular inclusions consist of benign mammary glands with an associated myoepithelial cell layer.
2. Mullerian-type glandular inclusions contain ciliated cells admixed with intercalated (peg) cells and are immunoreactive for PAX8, WT1, and ER.
3. Squamous epithelial inclusions are bland squamous-lined cysts or squamous nests.
4. Nodal nevi are capsular bland, spindled nevocytes that are immunoreactive for Melan A, Sox10, and S100 but are negative for HMB45.

EPITHELIAL INCLUSIONS

MAMMARY-TYPE GLANDULAR INCLUSIONS (HETEROTOPIC BREAST PARENCHYMA)

Mammary-type glandular inclusions (heterotopic breast parenchyma) have been described in axillary lymph nodes.[1,7–14] As most axillary lymph node sampling occurs in patients with primary breast carcinoma, the main diagnostic pitfall of benign mammary-type glandular inclusions is of course metastatic breast carcinoma (see **Box 2**, **Table 1**). Postulated mechanisms to explain the pathogenesis of mammary-type glandular inclusions include benign displacement or mechanical transport (eg, due to prior biopsy),[15–19] as well as the presence of ectopic mammary tissue or embryogenic malformation during development.[1]

Box 2
Pitfalls in the Diagnosis of Nodal Inclusions

- Nodal glandular inclusions are potential diagnostic pitfalls for metastatic ductal carcinoma; recognizing the presence of a myoepithelial cell layer (in mammary-type glandular inclusions) or ciliated and peg cells (in Mullerian-type glandular inclusions) aids in reaching the correct diagnosis.
- Nodal Mullerian-type glandular inclusions are potential diagnostic pitfalls for metastatic gynecologic tract carcinoma; recognizing the bland cytology, presence of cilia, and admixed intercalated cells aids in reaching the correct diagnosis.
- Axillary nodal nevi are a potential diagnostic pitfall for metastatic melanoma; recognizing the bland, spindled morphology and capsular locations of the nevocytes aids in reaching the correct diagnosis.

Pathologic Features

Microscopic foci of mammary-type glandular inclusions lack gross pathologic changes. Large, proliferative or cystic inclusions may be grossly visible as cystic spaces or solid, firm, tan and well-circumscribed nodules. Microscopically, mammary-type glandular inclusions are most commonly located within the lymph node capsule, but can occur in the node parenchyma (**Fig. 1**).[1] The inclusions can be solitary or multiple. Mammary-type glandular inclusions display a range of histologic appearances, from simple glands with low-cuboidal epithelium to those with apocrine metaplasia and microcysts, and to those containing architectural complexity including florid epithelial hyperplasia (**Fig. 2**),[20] adenosis,[21] and papillary proliferations.[1,22] The luminal epithelial cells are typically bland, with hypochromatic nuclei, inconspicuous nucleoli, and minimal mitotic activity. Mammary-type glandular inclusions have an associated myoepithelial cell layer (see **Box 1**),[7] which can be visible on hematoxylin-eosin (H&E) inspection alone, but also confirmed by immunohistochemistry (see **Fig. 2**; **Figs. 3–5**).

Atypical epithelial proliferations can involve, and most likely arise from, underlying mammary-type glandular inclusions. Ductal carcinoma in situ[14,23] and papillary carcinoma[23] have been reported within axillary nodal inclusions.

Differential Diagnosis

The primary differential diagnosis of mammary-type glandular inclusions in axillary lymph nodes is metastatic ductal carcinoma. Metastatic carcinoma typically involves the lymph node sinuses, in contrast to inclusions, which are most commonly located in the node capsule. However, as indicated previously, glandular inclusions can also occur in the node parenchyma. The differential diagnosis also includes other benign inclusions, specifically Mullerian-type glandular inclusions discussed later in this article, or metastatic well-differentiated adenocarcinoma of another primary site, such as lung or upper gastrointestinal tract.

Diagnosis

By immunohistochemistry, mammary-type glandular inclusions label like benign mammary glands. They are immunoreactive for pancytokeratin and CK7 and thus present a potential diagnostic pitfall if a cytokeratin is performed on a sentinel lymph node excision for breast carcinoma (see **Fig. 3**). The luminal epithelial cells are also immunoreactive for gross cystic disease fluid protein (GCDFP),