Benign Heterotopic Epithelial Inclusions in Axillary Lymph Nodes

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Benign heterotopic epithelial inclusions in axillary lymph nodes are an extremely rare condition that must be differentiated from metastatic carcinoma. We describe 2 histologically different examples of benign epithelial inclusions in nonsentinel axillary lymph nodes, each with an unusual clinical presentation.

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Benign epithelial glandular structures in or associated with lymph nodes have been infrequently documented at various body sites.1–14 Endometrial glands and “glands” derived from the mesothelial lining of the peritoneum in the para-aortic, pelvic, and inguinal lymph nodes,1–3 salivary glands and thyroid follicles in cervical lymph nodes,4 and mammary glands in the axillary lymph nodes5–14 are the most frequent examples of such inclusions. Distinguishing these benign glands from metastatic carcinoma is important for accurate staging and to avoid unnecessary treatment.

The histogenesis of glandular heterotopia is unknown, but it has been suggested that this phenomenon is most likely due to embryologic maldevelopment.1–14 Heterotopic mammary glands are characterized by the presence of a basement membrane and a myoepithelial cell layer. These constituents may be evident in routine hematoxylin-eosin (H&E) sections and may be confirmed by ancillary studies. In the absence of myoepithelial cells and basement membrane, glands in lymph nodes should be regarded as metastatic carcinoma even if the growth pattern is exceptionally well differentiated. Comparison of the primary tumor with the appearance of the intranodal gland is also an important aspect of this assessment.

REPORT OF CASES

Case 1

Clinical History.—A 33-year-old woman presented with a palpable lump present for 1 week in the upper outer portion of her right breast. The patient was otherwise healthy and had no significant medical or surgical history. She had stopped breastfeeding her first child approximately 3 months before the visit. She had no history of breast or skin disease. The results of a cervical cytology smear were negative.

Physical examination revealed a 1.0-cm, well-circumscribed, movable nodule in the upper outer quadrant of the right breast. Ultrasound revealed a solid nodule clinically suggestive of an intraparenchymal lymph node. At a 3-month follow-up visit, there was no change in the size of the breast nodule and an elective excisional biopsy was performed. The specimen consisted of a lymph node with a cyst surrounded by a rim of fibroadipose tissue. Fifteen months after surgery, the patient was well, with no evidence of masses or nodularities in either breast.

Pathologic Findings.—The tissue removed from the upper outer quadrant of the right breast measured 0.8 cm in greatest dimension. The bisected specimen revealed a tan nodule with a 0.2-cm cystic space containing yellow “caseous” material.

Routine H&E sections revealed a lymph node with normal nodal architecture and an intact capsule. Two subcapsular cystic intranodal epithelial inclusions were present (Figure 1, a and b). Both cystic inclusions were lined by a stratified squamous epithelium with a prominent granular cell layer. The larger cystic inclusion, corresponding to the focus seen grossly, contained keratin debris. A granulomatous reaction to cyst contents was focally present outside the cysts. The epithelium had rare mucin-filled vacuoles. The lymph node was surrounded by the adipose tissue, and no ductal or lobular units were seen.

Immunohistochemical Findings.—A myoepithelial cell layer was neither evident around the intranodal cyst in the H&E sections nor detected by immunohistochemical stains (smooth muscle myosin heavy chain, smooth muscle actin [SMA], or CD10) (Figure 1, c). No basement membrane antigen reactivity (collagen IV or laminin) was found around the cystic inclusions.

Case 2

Clinical History.—A 64-year-old woman had tubular carcinoma of the right breast diagnosed by needle core biopsy. Estrogen and progesterone receptors were reported as “strongly positive,” and Her2/neu oncoprotein was reported as “negative.” The patient underwent elective bilateral mastectomy consisting of a right modified mastectomy with right axillary lymph node dissection and a prophylactic left simple mastectomy with a left low axillary lymph node dissection. No residual carcinoma was seen in the right breast, and 18 right axillary lymph nodes were negative for carcinoma. The left breast showed no evidence of carcinoma. The left axillary lymph nodes were grossly unremarkable. The patient has no other significant medical or surgical history.

Pathologic Findings.—The right mastectomy had a palpable hematoma corresponding to the prior biopsy site. There was no gross evidence of tumor in the wall of the biopsy site. The lymph
Figure 1.  

*a,* Intranodal cystic epithelial inclusions. Subcapsular intranodal cystic epithelial inclusions are lined by a stratified squamous epithelium (hematoxylin-eosin, original magnification ×20).  

*b,* Higher magnification of the intranodal cystic epithelial inclusions seen in section a. The stratified squamous epithelium has a prominent granular cell layer. The largest cyst contains abundant keratin debris (hematoxylin-eosin, original magnification ×100).  

*c,* CD10 expression in the intranodal cystic epithelial inclusions. Complete absence of CD10 immunostain was noted around both cysts, indicating the lack of myoepithelial cell layer (immunoperoxidase method, original magnification ×100).

Figure 2.  

*a,* Intranodal heterotopic mammary ducts. A 1.0-mm aggregate of benign duct epithelium (arrow) was present in the subcapsular area of the axillary lymph node (hematoxylin-eosin, original magnification ×40).  

*b,* Higher magnification of ducts from the section a, showing 2 distinct cell layers (arrow) (hematoxylin-eosin, original magnification ×200).  

*c,* CD10 expression in the heterotopic mammary ducts. The CD10 immunostain strongly highlights the myoepithelial cell layer around all ducts (immunoperoxidase method, original magnification ×200).
nodes appeared grossly normal. The left simple mastectomy specimen was grossly unremarkable. Four small lymph nodes were found in the axillary tail.

No residual carcinoma was seen in sections from the biopsy site or elsewhere in the right breast. The 18 right axillary lymph nodes had no evidence of metastatic carcinoma. The left breast had fibrocystic changes without atypia. A 1.0-mm aggregate of ducts with an accompanying granulomatous reaction was found in the subcapsular region of 1 of 4 lymph nodes (Figure 2, a). In H&E sections, some ducts had 2 distinct layers consistent with epithelial and myoepithelial cells (Figure 2, b).

**Immunohistochemical Findings.**—Immunostains revealed stronger reactivity for CD10 (Figure 2, c) than for other myoepithelial cell markers (smooth muscle myosin heavy chain and SMA). Strong immunoreactivity for collagen IV and laminin highlighted basement membrane around the ducts.

**MATERIALS AND METHODS**

Paraffin-embedded sections were obtained for routine H&E sections and immunohistochemical analysis. Immunohistochemical staining was performed using the TechMate 500 automated immunostainer (Ventana Medical Systems, Inc, Tucson, Ariz) according to a modified MIP protocol (Ventana Medical Systems). Monoclonal antibodies to the following antigens were used: common acute lymphoblastic leukemia antigen—CD10 (56C6) and laminin (LAM-89) (both from Novocastra Laboratories, Ltd, Newcastle upon Tyne, England); collagen IV (clIV22) and SMA (1A4) (both from Dako Corporation, Carpinteria, Calif), and smooth muscle myosin heavy chain (Biogenex, San Ramon, Calif).

The ChemMate ABC peroxidase detection system (Ventana Medical Systems) was used for demonstrating collagen IV, laminin, smooth muscle myosin heavy chain, and SMA. The Cap-plus peroxidase detection system based on the labeled streptavidin-biotin method (Zymed Laboratory, Inc, South San Francisco, Calif) was used for demonstration of CD10. Before staining, paraffin sections were pretreated in a pressure cooker using cisco, Calif) was used for demonstration of CD10. Before staining, paraffin sections were pretreated in a pressure cooker using 10mM citrate buffer, pH 6.0 (CD10), in a water bath at 95°C for 40 minutes using antigen retrieval AR-10 (smooth muscle myosin heavy chain) or with 0.1% trypsin, pH 7.8, at 37°C for 10 minutes (collagen IV and laminin). Staining for SMA was performed without pretreatment.

**COMMENT**

The occurrence of benign epithelial inclusions in the axillary lymph nodes is a rare, well-documented event that has to be considered in evaluating axillary lymph nodes for metastatic carcinoma.5-11 Most reported examples of benign epithelial inclusions have been in patients without carcinoma, but coexistence with an invasive mammary ductal carcinoma of the ipsilateral breast has also been described.5,6 Cases reported in the literature describe predominantly 3 types of benign epithelial inclusions: cystic inclusions with a mostly squamous or apocrine papillary epithelial lining,7 tubules or ductlike structures reminiscent of mammary ducts,8 and lobules. Edlow and Carter9 reported the presence of more than 1 of these elements (admixture of apocrine papillary cysts and keratin-filled cysts) in 1 lymph node. Layfield and Mooney9 described an admixture of cystic inclusions lined by squamous epithelium with numerous ductlike structures; both elements showed strong immunoreactivity for myoepithelial antigens.

Our report illustrates 2 distinct types of benign epithelial inclusions. In the first case, the cystic epithelial inclusion was entirely composed of squamous epithelium with no ducts. Failure to detect evidence of myoepithelial cells suggests that the inclusions were derived from a cutaneous anlage rather than from mammary or skin appendage glands. We postulate that basement membrane components were obscured by the granulomatous reaction elicited by keratin debris. The possibility of metastasis from an occult squamous carcinoma is exceedingly unlikely in lymph nodes at this site, since no primary squamous carcinoma was found and the squamous cysts were well differentiated. The patient was well 15 months later.

In the second case, the lymph node inclusions were characteristic of heterotopic mammary glands, and this was confirmed by the immunostain results. These results illustrate the importance of immunohistochemical analysis in this circumstance. Metastatic spread from the right breast to the left axillary nodes would be very unlikely in the absence of right axillary node involvement. However, confirmation that glands in a left axillary node were heterotopic, rather than metastatic, was helpful in excluding the need for a search for an occult primary tumor in the left breast.

The differential diagnosis of benign heterotopic epithelial inclusions in axillary lymph nodes also includes nevus aggregates12 and macrophages,13 both of which may exhibit an epithelioid appearance. Nevus cell aggregates are characteristically located in the capsule of lymph node. The cells within the aggregates are similar to cells found in benign cutaneous nevi. Multinucleated macrophages (histiocytes) may also simulate epithelial structures, particularly in compressed subcapsular sinuses of lymph nodes. Careful histologic evaluation is essential to exclude metastatic carcinoma in all cases wherein a benign structure is in the differential diagnosis. Immunohistochemical confirmation of the diagnosis is recommended in histologically equivocal cases. Nevus cells are immunoreactive for S100 protein, the cells may contain melanin, and they are negative for cytokeratin. Macrophages are immunoreactive for CD68 and other histiocytic markers, the cells may contain debris, hemosiderin, and even suture material,14 and they are negative for cytokeratin.

**References**


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