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A Subset of Nondescript Axillary Lymph Node Inclusions Have the Immunophenotype of Endosalpingiosis

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Abstract

We report 2 cases of bland, otherwise nondescript axillary lymph node inclusions that have the immunophenotype of endosalpingiosis in patients with concurrent invasive breast carcinomas. Neither inclusion demonstrated the classic morphology of endosalpingiosis with admixed ciliated and secretory cells. Rather, both cases were composed of nondescript cuboidal to columnar bland epithelial cells situated within the lymph node capsule. Whereas both inclusions labeled diffusely for estrogen receptor and lacked evidence of a myoepithelial component, both labeled diffusely for PAX8 and WT-1, which distinguished them from their corresponding concurrent primary mammary carcinomas. These findings suggest that a subset of otherwise nondescript axillary lymph node inclusions represent endosalpingiosis and highlight the utility of PAX8 and WT-1 immunohistochemistry in distinguishing these from metastatic well-differentiated ductal carcinoma.

Keywords

lymph node inclusion; endosalpingiosis; sentinel lymph node; breast carcinoma

Benign epithelial inclusions in axillary lymph nodes are a well-recognized mimic of metastatic breast carcinoma.^{1–9} The main recognized types of inclusion are heterotopic breast epithelium (which demonstrates an intact myoepithelial layer), heterotopic cutaneous/adnexal epithelium (which often features cystic squamous epithelium), and rarely endosalpingiosis (which demonstrates admixed ciliated and secretory cells similar to fallopian tube mucosa). Aside from their distinctive morphologic features, all of these inclusions are typically centered on the lymph node capsule and have bland cytology, in

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contrast to metastatic breast carcinoma, which typically involves the sinuses and demonstrates greater cytologic atypia. However, there is abundant evidence that in some cases it is difficult to distinguish benign axillary lymph node inclusions from metastatic well-differentiated ductal carcinoma, particularly when the distinctive features of the inclusions are not well developed. First, some cases reported as node inclusions¹⁰ have been interpreted by others¹¹ as representing metastatic well-differentiated ductal carcinoma. Second, in *Rosen's Breast Pathology* textbook, the author references situations in which it is difficult to distinguish benign glandular inclusions from metastatic carcinoma and states that "metastasis derived from a primary breast carcinoma can only be excluded in this circumstance if a mastectomy is performed and the specimen is thoroughly studied."¹¹ Third, several of the reported cases of benign nodal inclusions were initially mistakenly diagnosed as metastatic carcinoma.^{10,12-14} In at least 2 reported cases, misdiagnosis of a benign inclusion as metastatic ductal carcinoma in a sentinel lymph node resulted in unnecessary axillary lymph node dissections.^{12,13}

Only a few cases of axillary or intramammary lymph node inclusions thought to be endosalpingiosis have been reported. Almost all of these have been morphologically typical cases of endosalpingiosis, characterized by ciliated columnar cells, secretory cells, and "intercalated (peg) cells" with clear cytoplasm.¹⁵⁻¹⁷ One case reported by Stolnicu et al¹⁸ did not demonstrate cilia but was extensively cystic and papillary, typical of endosalpingiosis. Other probable cases of endosalpingiosis reported previously have been described as "endosalpingiosis-like" in the absence of immunohistochemical markers to support the diagnosis of endosalpingiosis.^{13,14} More recently, several groups have used immunohistochemistry for Müllerian-specific markers to prove the diagnosis of nodal endosalpingiosis. Specifically, cases of typical nodal endosalpingiosis replete with ciliated and secretory cells have been demonstrated to label for WT-1 and PAX8, distinguishing them from the concurrent breast carcinomas.^{1,12} However, it is known that the 3 cell types of endosalpingiosis are present in varying proportions,¹⁹ and the number of ciliated cells in normal fallopian tube mucosa varies with the menstrual cycle and hormonal status; along these lines, some cases of endosalpingiosis in the abdominal cavity lack well-developed ciliated cells and instead are composed entirely of nondescript cuboidal to columnar cells. Therefore, it seems possible that some cases of axillary nodal endosalpingiosis could be occult, and characterized by nondescript glandular epithelium that (in the absence of myoepithelium) is difficult to distinguish from metastatic well-differentiated ductal carcinoma.

We report herein 2 cases of bland nodal inclusions, which we interpreted as nodal endosalpingiosis. In both cases, the concurrent invasive mammary carcinoma was of low nuclear grade and not easily distinguished cytologically from the inclusion. Neither inclusion demonstrated characteristic ciliated cells, raising the possibility of metastatic well-differentiated ductal carcinoma. However, in both cases the inclusions were intracapsular and strongly immunoreactive for PAX8 and WT-1, whereas the associated breast carcinoma was not, further supporting their distinction. These cases suggest that a subset of otherwise nondescript nodal inclusions, which are difficult to distinguish from metastatic well-

differentiated ductal carcinoma represent endosalpingiosis and highlight the utility of PAX8 and WT-1 immunohistochemistry in establishing this diagnosis.

MATERIALS AND METHODS

This study was approved by the institutional review board of the Johns Hopkins Hospital. The 2 cases in this study were derived from the consultation files of one of the authors (P.A.). Standard immunohistochemical analysis was performed on the axillary lymph node and breast tumor using the following markers: p63, smooth muscle myosin heavy chain (SMM-HC), estrogen receptor (ER), PAX8, and WT-1. The vendors and pretreatments are listed in Supplemental Table 1, Supplemental Digital Content 1, <http://links.lww.com/PAS/A219>.

RESULTS

Case Reports

The 2 cases are illustrated in Figures 1 and 2. Patient 1 was a 70-year-old woman who underwent a partial mastectomy for a 1.4 cm in situ and invasive lobular carcinoma with solid areas, Elston grade II of III (Figs. 1A, B). The primary tumor did not show vascular invasion. The 2 sentinel lymph nodes were negative for metastatic lobular carcinoma on hematoxylin and eosin and cytokeratin immunohistochemistry. However, one of the lymph nodes contained a bland intracapsular cytokeratin-positive gland, which was favored to be benign but was sent for consultation. Patient 2 was an 82-year-old woman who underwent partial mastectomy for a 1.7 cm in situ and infiltrating cribriform carcinoma, Elston grade I of III (Figs. 2A–D). This primary tumor did not show vascular invasion. The 2 sentinel lymph nodes were again negative for overt metastatic carcinoma, but each contained bland intracapsular glands, which were favored to represent benign breast inclusions but were sent for consultation.

Sentinel Node Inclusion Pathology

In both cases, the intracapsular lesions consisted of bland tubules with open lumens composed of cuboidal to columnar-shaped cells (Figs. 1C, D, 2E, F). The tubules consisted of a single layer of cells, and myoepithelial cells were not evident at their periphery. The tubules were cytologically bland, lacking mitotic activity or significant cytologic atypia. Whereas the cytology of the nodal tubules was similar to that of the invasive carcinomas of the breast in both cases, the architectures were different. Neither the linear, single file arrays or solid architecture of the invasive lobular carcinoma in case 1 nor the cribriform architecture that characterized the entirety of the invasive ductal carcinoma of case 2 was identified in the respective nodal tubules. Importantly, neither nodal lesion demonstrated evidence of ciliated cells, which would suggest endosalpingiosis.

In both cases, the nodal tubules showed no evidence of myoepithelial cells using immunohistochemistry for p63 and SMM-HC (Figs. 1E, 2G). Both labeled diffusely for ER, similar to the primary mammary carcinomas. However, in both cases, the nodal tubules were diffusely immunoreactive for PAX8 (Figs. 1F, 2H) and WT-1. In contrast, the primary breast carcinomas in both cases were negative for PAX8 (Figs. 1B, 2D), whereas there was

insufficient tissue to analyze for WT-1. On the basis of the immunohistochemical differences between the nodal lesions and the primary breast tumors, as well as their different architectures, we interpreted the nodal lesions as examples of endosalpingiosis. Clinical follow-up information is limited on these 2 patients. Patient 2 was treated with hormonal therapy only and shows no evidence of disease at 3 years follow-up. Patient 1 was lost to follow-up.

DISCUSSION

We report 2 distinctive cases of bland but nondescript nodal inclusions that demonstrated the immunohistochemical features of endosalpingiosis. Specifically, in contrast to their concurrent primary mammary carcinomas, these lesions labeled for Müllerian markers PAX8 and WT-1.

These cases highlight the importance of considering endosalpingiosis as a potential cause of glandular tissue involving axillary lymph nodes even when cilia are not seen. If one did not consider endosalpingiosis, one could view these lesions as well-differentiated, ER-positive epithelium lacking myoepithelial cells and thus indicate that one could not exclude the possibility that these nodal lesions represented a metastasis from an occult well-differentiated ductal carcinoma elsewhere in the breast. Indeed, some authors have suggested mastectomy as the only way to determine whether such nodal lesions lacking myoepithelial cells represent metastatic carcinoma or nondescript benign nodal inclusions.¹¹ However, using immunohistochemistry for Müllerian markers, we were able to demonstrate that these nodal lesions were distinct from the concurrent primary breast carcinomas and compatible with nodal endosalpingiosis. The etiology of endosalpingiosis remains debated, with possibilities including metaplasia of the secondary Müllerian system, lymphatic dissemination of fallopian tubal mucosa, implantation of sloughed fallopian tubal mucosa, and surgical displacement.¹² Whereas one or more of these may play a role in the pathogenesis of endosalpingiosis, the latter 2 are more difficult to reconcile with endosalpingiosis in supradiaphragmatic locations such as the axillary lymph nodes.

Prior studies have referred to axillary nodal inclusions with morphologic features of endosalpingiosis as “endosalpingiosis-like,” given that a specific immunohistochemical marker for endosalpingiosis was not available at the time of their description.^{13,14} More recently, several authors have utilized PAX8 and WT-1 immunohistochemistry to prove that cases with the typical morphology of endosalpingiosis in axillary lymph nodes truly represent endosalpingiosis.^{1,12} Our cases are distinctive in that the inclusions did *not* show the characteristic ciliated cells of typical endosalpingiosis and otherwise could potentially have been considered metastatic well-differentiated ductal carcinoma given their diffuse immunoreactivity for ER and absence of myoepithelial cells. We note that occasional cases of endosalpingiosis in pelvic/peritoneal sites can have ciliated cells that are difficult to identify or that may be absent altogether. The lesions reported herein in axillary lymph nodes are analogous to the latter lesions in the pelvis/peritoneum. What proportion of bland, nondescript axillary lymph node inclusions represents endosalpingiosis is difficult to determine, as these lesions are often small and in our attempts are often exhausted on the serial sections used for potential immunohistochemical characterization.

It should be noted that, besides metastatic breast carcinoma, the differential diagnosis for these nodal inclusions would include low-grade serous carcinoma of the ovary with metastasis to axillary lymph nodes or nodal involvement by a serous borderline tumor, which are recognized mimics of metastatic breast carcinoma.²⁰ The absence of architectural complexity and cytologic atypia in the current lesions, as well as the absence of a history of an ovarian tumor, helps dismiss this possibility.

Two main processes are hypothesized to result in benign epithelium in axillary lymph nodes: mechanical displacement of breast epithelium into the nodal sinuses and embryologic malformation resulting in inclusions in the capsule. Mechanical displacement of benign breast epithelium often emanates from a previously biopsied papillary lesion, and here the epithelium is present in the sinuses in association with hemosiderin-laden macrophages and degenerating red blood cells.²¹ The main recognized types of axillary nodal inclusions are heterotopic breast tissue, heterotopic cutaneous/adnexal epithelium, and endosalpingiosis. Heterotopic breast epithelial inclusions should demonstrate an intact myoepithelial layer with markers such as p63 and SMM-HC. Cutaneous/adnexal epithelial inclusions frequently feature squamous cysts, which are apparent on the hematoxylin and eosin sections. As discussed above, the diagnosis of endosalpingiosis can be supported by immunoreactivity for PAX8 and WT-1. Therefore, when encountering a potential axillary lymph node inclusion for which the differential is metastatic breast carcinoma, we recommend a limited immunohistochemical panel, given that these lesions are typically small and can be exhausted by attempts at extensive immunohistochemical analysis. We would recommend that the minimal panel include a myoepithelial marker (we favor a cytoplasmic marker such as SMM-HC over p63, as the latter can be discontinuous in benign epithelium and thus potentially falsely negative in a small benign breast inclusion) and a Müllerian marker (we favor PAX8 over WT-1, given that WT-1 may occasionally label mucinous and micropapillary breast carcinomas).²² ER immunoreactivity supports the diagnosis of benign breast inclusion or endosalpingiosis but does not distinguish either from a metastatic well-differentiated ductal carcinoma, which is almost always ER positive. GATA3 could potentially be useful in that it is positive in most ER-positive breast carcinomas and benign breast epithelium.²³ We would expect it to be negative in endosalpingiosis; however, we know of no formal study addressing this, although, in our experience, fallopian tube mucosa (the normal morphologic counterpart to endosalpingiosis) is negative for GATA3 (R.V., unpublished observations, 2014).

In conclusion, we report 2 distinctive cases of bland axillary nodal inclusions, which have the immunophenotype of endosalpingiosis despite lacking diagnostic ciliated epithelial cells. These cases illustrate the utility of including Müllerian markers such as PAX8 and WT-1 in the immunohistochemical workup of a potential axillary lymph nodal inclusion even if diagnostic morphologic features of endosalpingiosis are not present.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

Case 1. This patient's primary mammary carcinoma was a solid invasive lobular carcinoma (A), which as expected was nonimmunoreactive for PAX8 (note the benign lymphocytes in the upper left corner, which label as an internal control) (B). C and D, The sentinel lymph node contains an intracapsular glandular inclusion composed of a single layer of nondescript cuboidal to columnar cells. Ciliated cells are not evident. The nodal inclusion lacks evidence of a myoepithelial cell layer on SMM-HC immunohistochemistry (E) but demonstrates diffuse immunoreactivity for PAX8 (F).

FIGURE 2.

Case 2. A and B, This patient's primary invasive mammary carcinoma was an invasive cribriform carcinoma, composed of irregular cribriform nests and scattered tubules lined by bland, monotonous, cells with grade 1 nuclei. The invasive cribriform carcinoma lacked myoepithelium on SMM-HC immunohistochemistry (C) and as expected was nonimmunoreactive for PAX8 (D). E and F, The sentinel lymph node contained bland elongated tubules within its capsule. The inclusion was composed of bland columnar to cuboidal cells and lacked ciliated cells. The inclusion lacked evidence of a myoepithelial layer on SMM-HC immunohistochemistry (G) but demonstrated diffuse immunoreactivity for PAX8 (H).