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Invasive Mucinous Carcinoma Arising in Ectopic Axillary Breast Tissue: A Case Report and Literature Review

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Patient: Female, 70
Final Diagnosis: Primary invasive mucinous carcinoma arising from ectopic breast tissue
Symptoms: Axillary mass
Medication: Adjuvant hormonal therapy and irradiation to the ipsilateral axilla
Clinical Procedure: Wide local excision of ectopic breast carcinoma with lymphatic mapping and sentinel lymphadenectomy
Specialty: Surgery

Objective: Rare disease

Background: Invasive mucinous carcinoma arising in ectopic axillary breast tissue is an uncommon diagnosis. While some published medical literature makes recommendations regarding the management of ectopic primaries, many of these recommendations are outdated. We therefore hope to provide general guidance with the management of this rare entity.

Case Report: We report a case of a 70-year-old woman with primary invasive mucinous carcinoma of ectopic breast tissue. A literature study was performed on primary ectopic breast carcinoma. This case report with review of the literature was performed to provide rationales for a more conservative treatment based upon current data and treatment paradigms.

Although the diagnosis of primary ectopic breast carcinoma is uncommon, the presence of a suspicious nodule along the mammary ridge should alert the clinician to consider the possibility of this diagnosis. A mammogram and ultrasound of the nodule were performed and the suspicious nodule was biopsied, confirming the diagnosis. Breast conservation was performed with standard nodal evaluation.

Conclusions: The management of primary ectopic breast carcinoma should be based upon current breast conservation techniques of orthotopic breast cancer. Current data suggest that standard treatment paradigms remain applicable to this rare clinical entity.

MeSH Keywords: Adenocarcinoma, Mucinous • Breast Cancer • Breast Neoplasms • Mammary Carcinoma • Sentinel Lymph Node Biopsy

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Background

Ectopic breast tissue (EBT) can be defined as encompassing both supernumerary and aberrant breasts [1]. EBT is demonstrable in about 0.2–6% of the entire population [2–5]. For the sake of this discussion, EBT will be used to describe all breast tissue found distant to and/or noncontiguous with the normal anatomic breast.

Primary carcinoma of EBT is uncommon, making up only 0.3% of all breast neoplasms [6], with mucinous carcinomas representing a small fraction of these rare lesions. Since the published medical literature on ectopic breast cancers remains limited, and contains outdated guidelines for management, this case report is presented to provide general guidance on how to manage this rare entity.

Case Report

A 70-year-old gravida 1, para 1, post-menopausal African American woman presented to an outside institution complaining of a superficial right axillary mass that she first noticed 6 months prior to initial presentation. A mammogram was performed at an outside institution and found to be unremarkable. This was followed with a dedicated mediolateral oblique mammographic view of the ipsilateral breast and an ultrasound of the right axilla, which revealed a solid hypervascular, hypoechoic nodule protruding into the skin, measuring 1.0×0.6 cm (Figure 1). Differential diagnosis at the time included occult primary breast carcinoma, metastatic breast cancer, and various lesions of intradermal origin. She underwent an excisional biopsy of the axillary skin nodule, which demonstrated a 0.9-cm invasive mucinous breast carcinoma. The pathologic differential diagnosis at the outside facility included metastatic breast carcinoma *versus* primary adnexal tumor, with consideration given to a breast primary tumor.

Immunohistochemical analysis found that the tissue was estrogen receptor (ER)-positive at 99%, progesterone receptor (PR)-negative at <1%, HER2/neu-negative by fluorescence *in situ* hybridization, and negative for CK5/6, p63, and GCDFP-15. She was clinically staged according to American Joint Committee on Cancer (AJCC) 7th edition as pT1b, cN0, cM0. Her initial evaluation included a computed tomography (CT) of her chest, abdomen, and pelvis, which demonstrated no other lesions.

Her past medical and surgical history was unremarkable. She underwent yearly screening mammograms since the age of 40. Her family history was contributory for breast cancer in her mother at age 62, breast cancer in her daughter at age 47, and prostate cancer in her brother at age 71.

With positive margins on her initial excisional biopsy, the patient was referred to our institution. Pathology review confirmed the primary lesion as not being a metastatic focus or a small superficial lymph node, in part due to the absence of lymph node tissue and presence of surrounding healthy breast tissue adjacent to the cancer. The patient underwent a wide local excision of her surgical scar along with the subcutaneous tissue, and lymphatic mapping/sentinel lymphadenectomy (Figure 2). The sentinel lymph nodes felt clinically benign intraoperatively, and no enlarged lymph nodes were noted intraoperatively (Figure 3). Pathology demonstrated additional grade 1 invasive mucinous carcinoma within the residual subcutaneous EBT excised, but all margins were negative at a distance of ≥0.3 cm. There was no sentinel lymph node involvement, lymphovascular invasion, *in situ* component, or skin involvement on final pathology.

Postoperatively, she was prescribed external beam whole-breast radiotherapy of 46Gy, in 23 fractions, with a tumor cavity boost of 14Gy in 7 fractions. She was prescribed adjuvant endocrine therapy, and referred to genetics because of her significant family history of malignancy. The patient was seen 6 months postoperatively with no evidence of recurrence on examination.

Discussion

Embryology

Between the 5th and 6th week of embryonic development, the mammary ridges ("milk lines") begin to form as 2 ventral bands

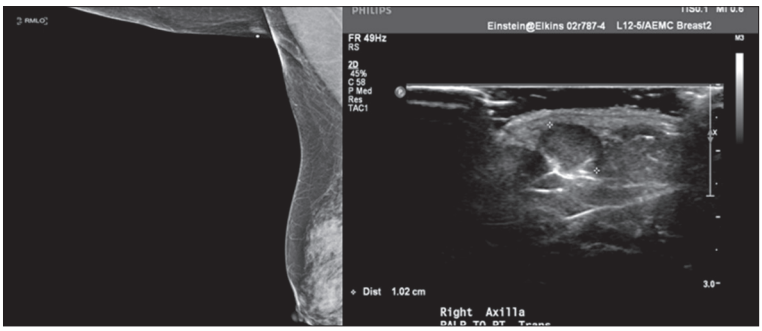

Figure 1. Preoperative imaging. Preoperative mammography noted no primary within the breast, while axillary ultrasound demonstrated a subcutaneous nodule that was subsequently noted to be a primary ectopic breast carcinoma.

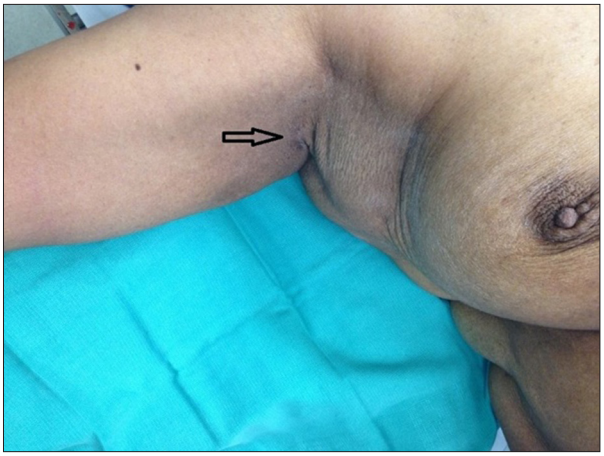

Figure 2. Operative site prior to incision. A small transverse incision is noted just lateral to the axillary crease. This was the site of the patient's initial excisional biopsy. This transverse incision was converted upon reexcision to a longitudinal incision to minimize contracture of the axilla.

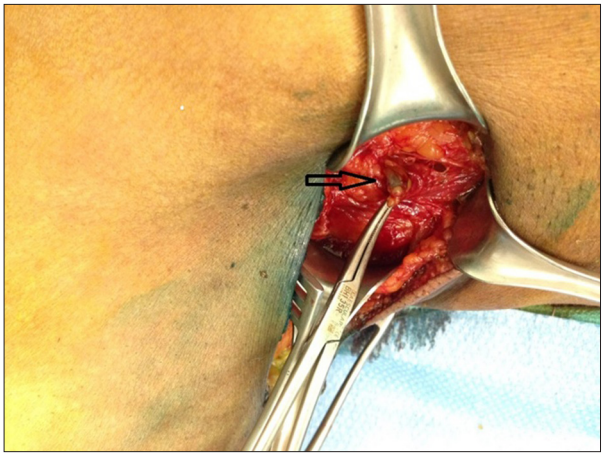

Figure 3. Sentinel node biopsy. The first sentinel node demonstrable at operation, visible here just deep to the tip of the hemostat.

of thickened ectoderm extending from the base of the forelimb (future axilla) to the hindlimb (inguinal region) [7]. If these fail to undergo complete regression soon after formation, polymastia (accessory mammary glands) or polythelia (accessory nipples) occurs [7]. Although the axilla is the most frequent site [1,6,8], EBT can be found in multiple locations in up to one-third of patients [8].

Clinical symptoms and manifestations

EBT is embryologically identical to normal anatomic breast tissue and is subject to normal hormonal responses, making it susceptible to the same diseases and neoplastic degeneration [7,9,10] as orthotopic breast tissue. Most patients first notice EBT as a soft, nontender mass in 1 or both axillae [10]. Although most EBT is asymptomatic [8,11], hormonal and cosmetic changes can be associated with menses, puberty, or pregnancy [7,9] and cause distension and mild pain [11], most frequently during the menstrual cycle [1,10].

Incidence and histology

Primary ectopic breast carcinoma (PEBC) of the axilla is rare and accounts for only 0.3% of all breast cancers [6]. The axilla is the most common site of PEBC, ranging from 58% to 71% [1,6] of cases. Mucinous carcinoma (MC), a rare histologic breast cancer subtype, is characterized by extracellular mucin [12] that dissects into the stroma [13], and accounts for <2% of all invasive breast cancers [13, 14]. In a series by Nihon-Yanagi of 64 patients with ectopic breast carcinoma, only 7.8% of patients had mucinous carcinoma, making the incidence of mucinous PEBC <0.2% of breast cancer cases. Other histologic subtypes found included invasive ductal carcinomas (75%), medullary carcinomas (7.8%), and apocrine carcinomas (6.3%) [15]. The mean tumor diameter was 2.8 cm (range 0.4–11 cm) and axillary lymph node involvement was present in 51.8% of patients [15].

Diagnosis

Due to the low incidence and misidentification of PEBC, the delay in diagnosis [16] averages 40.5 months [17], with lesions often mistaken for another disease such as a skin tag, nevus, hidradenitis, or lymphadenopathy [10]. EBT usually presents only a cosmetic concern [8], but this can be severe and a source of embarrassment. Nevertheless, it is subject to the same influences as orthotopic breast tissue; inflammatory and neoplastic conditions must be considered [3,7,16].

PEBC can present in several ways, ranging from normal-appearing ectopic breast tissue to a lesion having ulceration, bleeding, discolored skin, crusting, or associated discharge [15]. The presence of a subcutaneous mass along the mammary line should prompt the clinician to consider the possibility of PEBC [16] and the presence of suspicious nodules warrants histologic evaluation [8]. After surgical or needle biopsy confirms PEBC, some authors recommend further imaging to rule out metastatic disease or ipsilateral breast involvement [18]. A review of the literature suggests that ectopic breast tissue can be bilateral [6,19–21], and therefore contralateral evaluation should be strongly considered [6] via examination of the contralateral axilla, both breasts, and surrounding nodal basins [17].

Mammograms, in particular, may be negative because of the location of PEBC, while ultrasound may be of limited utility because of its frequent subcutaneous location. This can make the diagnosis uncertain and necessitate fine-needle aspiration (FNA) or core-needle biopsy [19]. In mucinous carcinoma of the breast, diagnosis may be challenging because of the likelihood of sampling areas of mucin that lack epithelial cells [13].

In a series of 26 patients undergoing resection of EBT, only 3.8% were found to contain a carcinoma [11]. While some authors suggest early prophylactic resection of ectopic breast tissue in any patient who presents with EBT for its oncologic, emotional, and anesthetic benefit [11,22], the low rate of PEBC may not justify the morbidity of such an approach. If the presence of EBT is painful or symptomatic, particularly during menses [11], complete excision can be performed for its cosmetic advantage and possible improvement of symptoms [10]. Prospective data regarding the benefit of such an approach is lacking and informed consent is imperative.

Others argue that given the lack of high-level evidence, resection of all asymptomatic EBT should be weighed against the risks of surgery [3,23,24] and recommend monitoring EBT with self-breast examinations and frequent follow-up visits [18,25]. In a series of 28 patients who underwent prophylactic excision [26], there was a 39.2% postoperative complication rate following excision of ectopic breast tissue, mostly related to poor scar formation followed by intercostobrachial nerve injury and presence of residual tissue. The high complication rate, however, suggests that patients with ectopic breast tissue should instead be counseled and conservatively managed [26]. Operative intervention in the axilla can also pose a risk of contracture and potentially lower the sentinel node identification rate [27].

Imaging evaluation

Mammography is usually not helpful in screening for PEBC because of its location in the high axilla [15,24], although oblique and exaggerated craniocaudal views may compensate for this location and visualize ectopic breasts [15]. Ultrasonography may also visualize ectopic breast tissue in the axilla and guide treatment based on radiologic features. Up to 21.2% of mucinous carcinomas of the breast are not detected on mammogram [28]. Most commonly, ectopic breast tissue carcinomas are sonographically hypoechoic, while mucinous carcinomas as a whole differ by having complex cystic and solid components [28], as well as internal hyperechoic features with hypoechoic peripheral shadows [15]. Heterogeneity and irregular margins on sonography confer a worse prognosis [28].

Routine preoperative breast MRI is controversial for orthotopic breast cancers and its role in PEBC is not well established. Some authors have suggested that MRI might exclude a primary ipsilateral occult primary breast carcinoma [16], or help with surgical planning by delineating the tumor's dimensions or extent of involvement [17]. Breast MRI demonstrates ipsilateral foci of breast cancer outside the quadrant of the primary in 1.7-14.6% of cases [29], but EBT represents a discontiguous area of breast tissue, analogous to a separate breast. Even among cases having extensive metastatic disease from PEBC, there are no reports of ipsilateral breast metastases [11], so there seems to be little role for MRI in preoperative evaluation to assess the ipsilateral breast. An occult primary breast cancer or ipsilateral breast metastases [30] should only be a concern if, after biopsy, pathologic evaluation is unable to distinguish a lymph node containing metastatic disease from an occult primary. If the lesion is a positive lymph node, MRI is appropriate to evaluate for an occult primary breast cancer if breast examination and imaging results are normal [31].

Staging

Currently, staging does not differentiate PEBC from orthotopic breast cancer, with the T classification based upon the maximal diameter of the PEBC [32]. Since EBT has a tendency to be more superficial, ectopic breast carcinoma is more likely to involve the skin and be classified as a T4 lesion [15], although the largest series in the literature demonstrates that small skin-involved lesions have similar prognoses as those without such involvement [33]. When comparing PEBC to orthotopic breast cancer, size and lymph node metastases have a similar relationship [15].

Axillary PEBC usually drains to the ipsilateral axillary nodes and from there, to the supraclavicular nodes [11,17]. Visconti et al. found that in all but 1 case of PEBC, nodal metastases disseminated to the ipsilateral axillary nodes [17]. In some reports, up to 46% of ectopic breast carcinomas found in proximity to the anatomic breast had ipsilateral axillary node metastases [1,32]. Other studies have found similar rates of nodal metastases from PEBC, and hypothesized that the increased rate of reported lymphatic involvement is due to diagnostic delay and differences in tumor biology [17], although this may be related to proximity, similar to the greater risk of nodal metastases from breast tumors of the upper outer quadrant [34]. Cogswell studied specimens obtained from patients who underwent radical mastectomies and autopsies of patients who died of distant metastases related to their PEBC and found no cases of ipsilateral breast involvement [11]. The isolated nature of PEBC and the linear relationship between tumor size and nodal involvement consistent with orthotopic breast cancers suggest that early recognition and segmental resection should remain mainstays of treatment [35].

Prognosis

Although EBT arises embryologically from the same origins as orthotopic breast tissue and may undergo similar pathological degeneration [9], data regarding long-term follow-up and treatment of PEBCs are scarce, necessitating individualization of management by the clinician.

Although a review of 171 cases diagnosed between 1865 and 1991 found that PEBC tends to effect women on average 6

years younger than orthotopic breast cancers [1], the diagnosis does not seem to confer a poorer prognosis by stage [1,36] nor a greater incidence of nodal involvement [15]. In a review by Nihon-Yanagi et al. of 68 patients, all but 1 was alive at a mean follow-up time of 28.3 months (range 2–156 months), with the only death attributed to pneumonia [15]. However, this is not universally accepted and others believe that a cancer is more likely in EBT [11]. One possibility for the disparity may be poorer outcomes in certain reports because of differences in clinical management or delays in treatment, rather than the disease itself [1].

Mucinous carcinoma (MC) of the breast

Mucinous carcinomas of the breast have less genomic instability and better disease-free survival, but have similar overall survival compared to invasive ductal carcinomas generally [12]. When comparing mucinous carcinoma with invasive ductal carcinoma, Bae et al. reported that 19% of mucinous carcinomas had axillary lymph node involvement and a lower N stage than invasive ductal carcinoma (IDC) in T1 and T2 lesions, but no significant difference was observed in late-stage tumors ($p<0.001$), greater expression of hormonal receptors (96%) than IDCs (67.7%), and a lower incidence of HER2/neu overexpression (5.2%) [12]. Despite the more favorable prognostic factors in MC [13], authors have concluded that nodal status and adjuvant therapy appear to be more significant predictors of prognosis than histologic type [12,36]. In a series of 11 400 cases of pure mucinous breast carcinoma, patients tended to have a better overall and disease-free survival [36], while only 12% had lymph node involvement and most expressed other favorable prognostic indicators such as ER (94.1%) and PR (81.5%) [36].

Treatment

Due to its rarity and paucity of data, there is little published medical literature on management of axillary PEBC [17,24], but standard breast cancer paradigms still apply. Historically, PEBC was treated with excision of the ectopic breast tissue carcinoma, radical mastectomy, and radiation to the chest [11, 17]. As far back as 1961, Cogswell and Czerny found no oncologic benefit to performing a radical mastectomy over excision of the axillary tumor and tail of the breast, and axillary lymphadenectomy [11]. In a study of 90 cases of PEBC, radical or modified radical mastectomy offered no survival advantage over wide local excision with lymphadenectomy or adjuvant radiation [6], demonstrating that routine ipsilateral prophylactic mastectomy should not be recommended [1,24].

As therapies evolve and we learn more about tumor biology and behavior, the surgical management of breast cancer is becoming less morbid. Since 2001, the preferred treatment of PEBC has been wide local excision, axillary lymphadenectomy, adjuvant radiation, and chemotherapy and/or hormonal therapy [17,19,24]. Currently, adjuvant therapies such as anthracycline-based chemotherapy, hormonal therapy, and irradiation are being used in the adjuvant setting to lower recurrence rates and improve the survival patients with PEBC [41]. Given that histological data confirms that these are breast cancers, we believe the best treatment practices of orthotopic breast cancer should be applied to PEBC [1].

Patients with hormone receptor-positive PEBCs should be offered adjuvant hormone therapies because of its reduction of contralateral breast cancer [38] and recurrence rate advantage, also seen for mucinous tumors such as that reported here [39]. Adjuvant therapy should be based upon stage, with gene expression profiles considered, as with orthotopic primaries [39], although data is lacking. Trastuzumab therapy should also be considered, but for mucinous tumors, reports suggest that trastuzumab resistance occurs because of a protective barrier created by their high mucin content [40].

Questions regarding irradiation fields remain unanswered. Although some authors recommend irradiating the tumor cavity, axilla, and ipsilateral breast [37], disagreement exists, and reports of treating the axilla and primary site alone have been published [24,32,41]. Despite its propensity for early lymphatic involvement, metastatic spread to the ipsilateral breast has not been reported [11,15,32]. There is little reason to believe that PEBC without ipsilateral breast involvement necessitates adjuvant irradiation beyond the tumor site and axilla, and all available evidence suggests that radiotherapy need not be used on the ipsilateral breast [41].

Axillary dissection can result in significant morbidity. In 1 series, physical and psychological complications were reported in most (73%) patients who underwent axillary dissection [42]. Currently, lymphatic mapping and sentinel lymphadenectomy are standard practice and highly accurate [43]. There are few reports describing the use of sentinel lymphadenectomy in the treatment of ectopic breast cancer [32,44,45]. In this case report, we were able to utilize sentinel lymphatic mapping along with sentinel lymphadenectomy in identifying 3 sentinel lymph nodes, avoiding the potential morbidity of axillary lymphadenectomy. Because sentinel node biopsy is successful in both breast cancer [44] and melanoma [46] (among other malignancies), from a variety of anatomic locations, there is no biologic reason to believe that this would be different for PEBC.

Thorne et al. used sentinel lymphadenectomy to isolate the lymphatic drainage of accessory breast tissue on the anterior abdominal wall. They reported more accurate staging and suggest utilizing lymphatic mapping and sentinel lymphadenectomy for PEBC [45]. PEBC is found to be close to the normal

anatomic breast in 93% of cases [1], which makes use of radionuclide potentially more challenging because of the proximity of the primary injection site to the location of the nodes with shine-through from the primary, potentially obscuring the lower gamma counts from nodes. However, this proximity should also make the lymphatic drainage patterns somewhat predictable, and use of blue dye remains practical, as in this case. We therefore believe that the use of the sentinel lymph node technique, using blue dye such as Lymphazurin, is safe and feasible in patients with early-stage PEBC. When blue dye is injected, intradermal injection may be required because of the subdermal nature of the lesion in the axilla; injection into the axilla would stain much of the tissue and make sentinel node identification difficult. Should radionuclide be desired, resection of the primary would be required prior to the search for sentinel nodes, to prevent shine-through and allow for detection by the gamma probe adjacent to the area of the PEBC [47].

Surveillance

There are no specific surveillance guidelines for PEBC, but follow-up involving serial examinations should be maintained [17,24]. The American Society of Clinical Oncology (ASCO) clinical practice guidelines [48] and NCCN Guidelines [49] for breast cancer follow-up and management after primary treatment can be used in patients treated for PEBC, and standard bilateral mammographic screening should be performed annually. The site of the resection, however, is likely to be primarily amenable to physical examination, with imaging required only in the event of a physical examination finding.

Conclusions

Due to its rarity, management guidelines for invasive mucinous carcinoma of ectopic axillary breast tissue are lacking.

Once the diagnosis of PEBC is confirmed, multi-disciplinary treatment should be employed based upon current breast cancer guidelines. We believe that early-stage PEBC can be treated with wide local excision, sentinel lymph node biopsy, and axillary dissection if required. The limited published data also suggest that radiotherapy should be limited to the tumor cavity and ipsilateral axilla. The patient should be prescribed hormonal therapy and/or chemotherapy, depending on the tumor characteristics, all consistent with standard breast cancer guidelines.

Conflicts of interest

All authors declare no conflicts of interest.

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