

Breast cancer presenting in aberrant axillary breast tissue

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Aberrant axillary breast tissue may occur anywhere along the embryonic mammary streak. This tissue responds to hormonal influences and is at risk for breast disease, paralleling the anatomically correct breast. A paucity of information exists regarding treatment of patients with cancer of aberrant breast tissue. We report our experience with one case and review the literature.

Case history

The patient is a 53-year-old, gravida 2, para 2, perimenopausal white female who presented with a history of a mass in the left axilla of several months' duration. The mass was occasionally tender, but the tenderness was not related to her menstrual periods, which she continued to have regularly. There was no evidence that the mass was enlarging, nor were there any breast symptoms.

History

The patient was 33 years old when she gave birth to her first child. Her family history was negative for breast or ovarian cancer in a primary relative. In 1997, she underwent a needle localization right breast biopsy for indeterminate microcalcifications. Pathologic examination revealed atypical lobular hyperplasia. In 1999, she was given the option of taking tamoxifen for chemoprevention because of the

finding of atypia on a previous biopsy. She decided against this medication and opted instead for close follow-up alone.

Physical examination and imaging

On physical examination, the breasts were normal to inspection and palpation bilaterally. The right axilla was negative. Examination of the left axilla revealed a 6-mm subcutaneous moveable mass, which was tender to palpation. Mammography of both breasts showed benign-looking microcalcifications, which were stable, and a stable benign intramammary lymph node in the left breast. Ultrasonography of the left axilla demonstrated a 6-mm hypoechoic mass within the subcutaneous tissue, compatible with a sebaceous cyst (Figure 1).

Laboratory studies

An excisional biopsy was performed. The pathologic specimen consisted of skin and underlying tissues. On histologic examination, the overlying epidermis and superficial dermis were normal. The subcutaneous adipose tissue demonstrated ectopic breast tissue composed of lobules and ducts. Within this tissue, a nodule of infiltrating ductal carcinoma, grade II, measuring 0.8 cm, was identified. An intraductal component, comprising less than 2% of the tumor, was



FIGURE 1 Sonogram of left axillary mass demonstrating a 6-mm hypoechoic nodule.

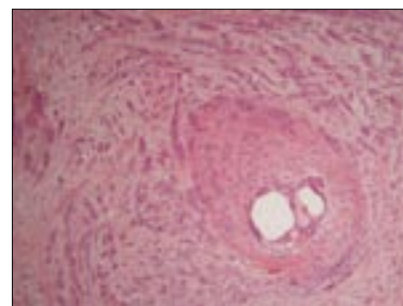


FIGURE 2 Infiltrating ductal carcinoma, Bloom-Richardson grade II, adjacent to a distorted sebaceous gland of axillary skin.

present. The tumor extended upward to involve the deep dermal structures. Margins were positive. Estrogen and progesterone receptors were positive; HER2/*neu* was not overexpressed (Figure 2).

Staging studies, including chest X-ray films and laboratory studies, showed no evidence of distant disease. The patient also underwent magnetic resonance imaging (MRI) of both

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breasts to exclude other foci of disease. The MRI scans were normal.

Sentinel node biopsy

The patient returned to the operating room for re-excision and sentinel node biopsy. The re-excision showed no evidence of residual tumor. The sentinel node biopsy was performed by injecting a radionucleotide in the retroareolar region and isosulfan blue dye in both the retroareolar region and around the tumor in the axilla. A blue-stained lymphatic channel was clearly identified and traced back to a blue-stained node, which was also radioactive. This node was removed. On pathologic examination, there were three nodes in this cluster, all negative for tumor.

Consultations were obtained from two radiation oncologists and a medical oncologist. The patient received radiotherapy to the breast and the primary site in the axilla. Following completion of radiotherapy, she began taking tamoxifen. She is currently disease free at 1 year.

There were two critical questions in formulating a treatment plan for this patient:

1. Should radiotherapy be given and, if so, should the breast be included or just the primary site in the axilla?
2. Could a sentinel node biopsy be technically accomplished in this situation and, if so, would it be reliable?

Two opinions regarding the issue of radiotherapy were obtained, one of which was from a national expert in radiotherapy for breast cancer. Despite the paucity of information in the literature, both opinions concurred that radiotherapy to the ipsilateral breast with a boost to the primary site in the axilla was indicated.

In the initial description of sentinel node biopsy, prior surgery in the axilla was considered a relative contraindication.¹ More recent studies, however, have shown accuracy in locating the sentinel node in patients with prior axillary surgery for malignancy or other unrelated benign conditions.² With the location of the primary tumor in the axilla, radionu-

clide injection would create unacceptable shine-through. For that reason, it was elected to inject the radionucleotide and a portion of the isosulfan blue dye into the retroareolar region. Studies have shown results from injection in this location to be as accurate as those from peritumoral injections.³ However, one also had to consider that the drainage of a primary tumor within the axilla might be different from one in the breast. Therefore, a small amount of isosulfan blue dye was injected around the tumor. Both tracer materials went to the same node.

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About this rare cancer

Normal human mammary development begins at 4-5 weeks with the emergence of a two- to four-cell layer ectodermal mammary streak located laterally on the embryonic trunk and extending from the axilla to the groin. By the time the embryo is 20-mm long, regression of most of this streak occurs, whereas tissue in the pectoral region remains, forming the mammary ridge.¹ This primordial ectoderm then extends into the mesenchyme, developing small buds which canalize to form the ductal system of the breast.^{2,3}

In about 1%-2% of the general population, incomplete regression results in anomalous breast tissue,

which may remain anywhere along the original mammary streak. Occurrence of aberrant breast tissue is most frequent in the axillary region.⁴ This aberrant tissue may consist of any combination of nipple, areola, and glandular tissue or only a patch of hair.

Terminology

Terminology has not yet been standardized in the literature. Initial classification by Kajava in 1915 specified the ectopic breast as with or without a nipple, areola, and/or glandular tissue (Table 1).^{2,5} The ectopic breast has been more recently described by differentiating between polythelia (accessory mammary gland remnants of mammary streak regression associated with

urologic abnormalities) and aberrant glandular tissue (tissue without a ductal system or relationship to the overlying skin) usually found in proximity to the ipsilateral breast and unassociated with other anomalies (Table 2).^{3,4}

Polymastia is defined as having more than two breasts. Sixty-five percent of women with polymastia have one additional location, and 30% have two additional locations; in addition, rare reports exist of more than four breasts.⁶ Polythelia has been linked to genitourinary abnormalities and may have a genetic foundation in at least some cases, having been reported to occur in multiple family members.^{7,8} Ectopic breast tissue refers to supernumerary and aberrant breast tissue. The incidence ranges from 0.6% to 6.0% and is highest among Japanese newborns, compared with other racial/ethnic groups.

Clinical manifestation and pathology

Ectopic breast tissue may appear as anything from subcutaneous tissue similar in appearance to a small mole to that of a fully functioning breast.⁴ Histologically, the supernumerary breast may have an organized ductal system to the external skin, whereas aberrant breast tissue alone has no such ductal development and is not connected to the ipsilateral breast. Both supernumerary and aberrant breast tissue may be overlooked due to their small size. However, this tissue is subject to normal hormonal controls and may become clinically apparent as females enter puberty or during pregnancy. Ectopic breasts with a complete areolar complex will function as normal breasts, including lactation. Symptoms in axillary breast tissue reportedly worsen with subsequent pregnancies, causing increased pain and local irritation.^{1,3} However, some studies suggest that the tissue may be asymptomatic.⁶

Diagnosis

Ectopic axillary breast tissue is frequently bilateral. When discovered, it should prompt evaluation for a contralateral counterpart.⁹ As with any mass, tissue diagnosis is required. Early diagnosis of carcinoma in ectopic breast tissue requires early tissue diagnosis since the clinical diagnosis is unreliable.⁹ If unaccompanied by a nipple-areolar complex, the mass may be misdiagnosed as a lipoma, lymph node, sebaceous cyst, or hidradenitis suppurativa.^{6,7}

Ectopic breast tissue is at risk for benign and malignant breast disease. Reported diagnoses include fibrocystic disease, mastitis, fibroadenoma, atypical hyperplasia, and carcinoma.¹⁰ The most frequently reported malignant disease is infiltrating ductal carcinoma (79%), followed by medullary and lobular carcinoma (9.5%).⁴ Rare reports of Paget's disease,¹¹ cystosar-

TABLE 1

Classification of aberrant breast tissue (Kajava)

Group	Type	Terminology	Description
Glandular tissue with all or part of the nipple-areolar complex	I	Polymastia	Complete breast: nipple, areola, glandular tissue
	II	Supernumerary breast (without areola)	Nipple and glandular tissue
	III	Supernumerary breast (without nipple)	Areola and glandular tissue
Glandular alone	IV	Ectopic breast tissue	Glandular tissue only
Part of nipple-areolar complex alone	V	Pseudomamma	Nipple and areola only; fat replaces glandular tissue
	VI	Polythelia	Nipple only
	VII	Polythelia areolaris	Areola only
	VIII	Polythelia pilosis	Patch of hair only

TABLE 2

Aberrant breast tissue is distinct from polythelia

Diagnosis	Location	Description	Associated anomalies
Polythelia	Regressed mammary streak	Accessory nipples	Urologic anomalies
Aberrant breast tissue	Usually near ipsilateral breast, but without any histologic connection	Glandular tissue; no association with skin or ductal development	No other associated anomalies

coma phyllodes,¹⁰ papillary carcinoma,¹² leiomyosarcoma,¹³ and invasive secretory carcinoma¹⁴ also exist.

In a 1994 review of 82 cases of ectopic breast cancer, Marshall et al⁴ found an increased incidence of cancer in aberrant breast tissue but no increased incidence in cancer within supernumerary breasts. Prior studies have not always differentiated between these two forms of ectopic breast tissue. Ectopic cancers located in the axilla present with more extensive disease at an earlier age, suggesting that aberrant breast tissue may be at increased risk for malignant change.^{3,4,9} Other studies have shown no such increased risk.^{1,6} One study of axillary accessory breast tissue diagnosed by fine-needle aspiration found only 2 possible cases of cancer out of 69 cases,⁶ and a separate study of axillary aberrant breast tissue removed for cosmetic purposes found no cancer in 28 cases.¹

Staging

Staging of carcinoma of aberrant breast tissue should be based on a comparison with TNM staging of the anatomically correct breast. The low incidence of ectopic breasts, combined with an unknown distinction between the disease processes of supernumerary and aberrant breast tissue, make the prognosis unknown. Prognosis and treatment based on previous cases are difficult to establish based on limited data and poor follow-up reporting.

Lymph node involvement

Lymphatic exploration is based on the location of the ectopic breast and known patterns of drainage, as described by Sappey.¹⁵ Lesions above a 2-cm wide, circumferential periumbilical band at the 12th rib are predicted to drain to the axillary nodes, whereas lesions below this band are predicted to drain to the inguinal nodes. Midline lesions may drain to

bilateral axillary or inguinal nodes.

Lymphatic drainage of the ectopic breast may be unpredictable. In one review, 46% of aberrant breast carcinomas found in proximity to the anatomic breast had ipsilateral axillary metastases. Invasion of the internal mammary chain is possible. Bilateral axillary metastases from midline cancer have also been reported.⁴ Metastatic spread to the ipsilateral breast has not been reported.

Management

Marshall et al⁴ advise that surgical management should follow current treatment recommendations for parallel TNM-classified breast cancers. Ectopic tissue should be excised completely, with nodal excision as indicated.⁴

Summary

Ectopic axillary breast tissue may be more common than we appreciate. Once identified, this tissue at risk for cancer must be followed for development of breast disease similar to anatomically correct breast tissue. Evaluation for a contralateral tissue counterpart is necessary. Cancer in ectopic breast tissue is rare but, once di-

agnosed, should be staged and treated following current recommendations for TNM-staged breast cancers, with excision and lymph node evaluation as indicated.

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Ectopic breast cancer: rare, treatable, and potentially curable

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THE CASE DESCRIBED by Jennifer Bakker and her colleagues is a rare instance of an invasive breast lesion that developed in ectopic breast tissue. To make this diagnosis, it is important to understand the development of ectopic breast tissue and to consider

a careful differential diagnosis of an axillary mass.

Embryogenesis of ectopic breast tissue

Embryonic breast development begins during the fourth week of gestation, when ectodermal tissue forms a ridge along the ventral surface ex-

tending from the axilla toward the midline of the groin. This ridge is called the mammary ridge, or "milk line." In normal breast development, the mammary ridge recedes, leaving only bilateral mammary tissue at the fourth intercostal space. However, if the ridge recedes incompletely, ectopic breast tissue can remain. This

tissue is separate from the tail of the breast. The remnant tissue can be left anywhere along the milk line. Although the axilla is the most common site, residual breast tissue has been reported at parasternal, subscapular, and labial sites.¹ The remnant tissue may reveal itself as a nipple/areola with mammary tissue, as a nipple, as an areola, or as mammary tissue.

Polythelia—the presence of supernumerary nipples—is apparent at birth and is a fairly common congenital anomaly. Its incidence has been reported as anywhere from 1:100 to 1:500 and is more common in Asian (3.7%),² African-American (1.63%), and Jewish (2.5%) neonates than among Caucasian newborns (0.22%).³ Polythelia may be associated with other congenital defects, including cardiac conduction abnormalities and renal anomalies.⁴

Polymastia—the presence of a supernumerary breast—is usually apparent at birth because of the nipple; however, the mammary tissue is dormant until puberty, when menstrual cycling may cause the tissue to increase in size and become tender. Some supernumerary breasts are functional and capable of lactation.

Unlike polythelia and polymastia, in which a nipple or areola is visible, ectopic breast tissue may not become apparent until puberty or pregnancy, when the breast tissue responds to hormonal fluctuation. In some case reports, the axillary ectopic breast tissue did not become apparent until the tissue enlarged during a first or second pregnancy.¹ Ectopic breast tissue is also known as aberrant breast tissue and is not functional because it does not have a ductal communication with the skin. The incidence of axillary ectopic breast tissue in women has been reported to be as high as 6%.⁵ Ectopic breast tissue is bilateral in

30% of cases. Consequently, it is important to evaluate the opposite side once axillary ectopic breast tissue has been discovered.

Development of ectopic breast cancer

Ectopic breast tissue is at risk of developing any benign or malignant condition that can develop in a normal breast. Fibrocystic disease,⁶ atypical hyperplasia, Paget's disease,⁷ and invasive ductal⁸ and invasive lobular⁹ carcinomas have all been reported in axillary ectopic breast tissue. The incidence of ectopic breast cancer has been estimated at 0.3% of all breast cancers.¹⁰ Some authorities believe that a malignancy is more likely to develop in ectopic breast tissue than in normal breast tissue.

Marshall et al¹¹ reviewed a series of 82 cases of ectopic breast cancer published between 1865 and 1994. The mean age at diagnosis of patients with ectopic breast cancer was 54—about 6 years younger than the average age when cancer arises in normal breast tissue. Fifty-eight percent of the cases of ectopic breast cancer were located in the axilla, and the majority were in proximity to normal breast tissue. In all, 79% of the cases of ectopic breast cancer were invasive ductal carcinomas, and 9.5% were medullary or lobular invasive carcinomas. Forty-six percent of the patients with ectopic breast cancers in the axilla had ipsilateral axillary lymph node metastases. Metastasis to the ipsilateral normal breast tissue was not documented in any of these cases.

With so few cases of ectopic breast cancer reported, it is difficult to say whether there is truly an increased risk of malignancy or this is more a result of reporting bias. What is known, however, is that ectopic breast cancer seems to have a worse prognosis than cancer occurring in the normal breast.

The largest case series to date was reported by Evans and Guyton in 1995.¹⁰ They collected 29 references in the literature from 1929 to 1993, in which 90 cases were discussed. Of these 90 cases, 64 were located in the axilla. Follow-up was limited and available for only 42 cases, half of which had recurred within 12 months. There were six long-term (> 4 years) survivors. Four were treated with axillary mastectomy and either lymph node dissection or axillary radiation therapy. Of these patients, only one received adjuvant chemotherapy. Two of the six were treated with radical mastectomy of the axillary tissue and an ipsilateral normal breast. There appeared to be no survival benefit to radical mastectomy over axillary mastectomy with either axillary lymph node dissection or adjuvant radiation therapy.

The worse prognosis of ectopic breast cancer was thought to be secondary to several factors. First, because this is such a rare form of cancer, its diagnosis is often made late, after the breast cancer had already metastasized to the lymph nodes in the axilla. Second, because the primary tumor is located in the axilla, it may spread to the axillary lymph nodes more quickly. However, if these cases of ectopic breast cancer are matched with pectoral breast cancer by stage, they seem to have a similar course, except that axillary ectopic breast cancers are diagnosed at a later stage.

Treatment considerations

At present, treatment of ectopic breast cancer is based on the same TNM staging of normal cancer. Surgical resection of the ectopic tumor, as well as exploration of local nodal groups, is recommended. In addition, care should be taken to rule out any evidence of lymph node tissue surrounding the ectopic tissue to ensure that the tumor

is not simply an involved axillary lymph node arising from a primary tumor in normal breast tissue. Magnetic resonance imaging (MRI) of the normal breasts, as was done in the accompanying case report, is an important diagnostic component to rule out any underlying malignancy of normal breast tissue. Given the usual proximity of ectopic breast tissue to the axillary nodes, there is a 46% incidence of nodal metastasis, based on prior case reports. An ipsilateral prophylactic mastectomy performed in the presence of a well-documented ectopic tumor has not been shown to offer a significant survival advantage over resection of the ectopic breast mass and involved lymph nodes and is usually not recommended.

To date, there are no published series of case reports that evaluate the use of chemotherapy or radiation therapy in the treatment of ectopic breast cancer; only individual case reports exist. Estrogen receptor, progesterone receptor, and HER2/*neu* expression status have not been reported in the two largest case series.^{10,11} Those patients with node-positive disease are treated the same way as patients with pectoral breast cancer and node-positive disease are treated.

The more difficult question to answer is how to treat women with ectopic axillary breast cancer and *node-negative* disease. Given the proximity of ectopic breast tissue to the axillary lymph nodes, adjuvant chemotherapy followed by irradiation and antihormonal therapy (depending upon the hormone-receptor status of the tissue) would not be an unreasonably aggressive approach. Roorda et al⁸ successfully treated a 70-year-old woman with a 3-cm left ectopic axillary breast cancer with no known lymph node metastasis with surgical excision, irradiation, and 7 years of adjuvant

tamoxifen therapy, with no evidence of recurrence in 9 years. However, until we have more case series that report the experiences of others, we will not know the optimal way of treating these patients.

Adjuvant irradiation to the site of the ectopic axillary tumors and lymph nodes, as was performed in the case described by Bakker et al, should be considered for all of these patients. The role of irradiation to the ipsilateral normal breast is not clear. Marshall et al¹¹ reported that none of the ectopic breast cancers spread to the ipsilateral breast; however, there were later recurrences of breast cancer in the ipsilateral breast in three patients.¹¹ Whether or not these three cases were instances of new primary breast cancers is unclear.

The decision to include ipsilateral breast irradiation as part of adjuvant therapy should be based on the level of certainty of the diagnosis of an axillary ectopic breast mass. This decision should include accurate pathologic interpretation of the tumor to exclude surrounding lymph node tissue and screening information derived from breast ultrasonograms and MRI scans to ascertain the possibility of a primary tumor within the normal breast. If any level of uncertainty exists about the nature of the ectopic origin, then ipsilateral breast irradiation should be included as part of the treatment plan.

Conclusion

Ectopic breast cancer is an exceedingly rare form of breast cancer; however, as Bakker and colleagues reveal, it is an important one to keep in the differential diagnosis of an axillary mass. Even given their proximity to axillary lymph nodes, these cancers appear to be highly treatable and potentially curable when found early. Primary local treatment remains surgical excision with exploration of the

lymph nodes. Adjuvant radiation therapy should be considered with irradiation to the axilla. The benefit of irradiation of the ipsilateral breast is less clear and not well studied. Adjuvant chemotherapy and hormonal therapy should be considered based on TNM staging and hormone-receptor status.

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