The presentation of contralateral axillary lymph node metastases from breast carcinoma: a clinical management dilemma

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Abstract: Metastases to the contralateral axillary lymph nodes in breast cancer patients are uncommon. Involvement of the contralateral axilla is a manifestation of systemic disease (stage IV) or a regional metastasis from a new occult primary (T0N1, stage II). The uncertain laterality of the cancer responsible for these metastases complicates overall disease staging and is a management dilemma for clinicians. Seven women who developed contralateral axillary metastases (CAM), but did not have evidence of systemic disease were identified. Patient demographics, histopathologic tumor characteristics, treatment and outcome were examined. The median age was 49 years. A family history of breast cancer was present in six (86%). The initial breast cancers were located in all quadrants. They were generally hormone receptor negative, HER-2/neu overexpressing and associated with lymphovascular invasion. There was a median interval of 71 months between initial breast cancer diagnosis and CAM presentation. Surgical management of the CAM included simple excision in one (14%) and axillary lymph node dissection in five (71%). Adjuvant treatment consisted of chemotherapy in seven (100%) and hormonal therapy in one (14%). The median follow-up from the diagnosis of CAM was 35 months and three women were alive without disease, two were alive with disease and two had died of disease. With surgical treatment, there were no axillary recurrences in this series. When patients present with CAM and no evidence of systemic disease or a new primary in the contralateral breast, surgical treatment should be considered for local control and possibly improved relapse-free survival.

Key Words: axillary recurrence, breast cancer, contralateral axillary lymph node metastases, lymphatic drainage, staging

The presentation of contralateral axillary lymph node metastases following prior treatment of a unilateral breast cancer is uncommon with a reported incidence between 3.6% and 6% (1). This has been considered to be stage IV disease as the cancer has crossed the midline and metastasized from the original site. Traditionally, CAM has been treated with systemic therapy, either chemical or hormonal. However, this may be a new, occult primary in the opposite breast (T0N1, stage II). Identification of a new cancer would motivate a different treatment, either a mastectomy or breast conservation therapy following an axillary lymph node dissection. It is this uncertainty of stage which presents a management dilemma for clinicians.

When a cancer is found in the contralateral axilla of a woman either currently or previously having been treated for cancer in the opposite breast, there are three possible sources. The malignant focus may represent a metastasis from an occult primary in the ipsilateral breast, as a woman with a personal history of breast cancer is at increased risk of developing a second breast cancer. Secondly, it may represent contralateral spread from the original breast tumor. Lastly, the tumor may represent a metastasis from an extramammary site. These include adenocarcinoma of the uterus, gastrointestinal tract, ovary, thyroid, kidney; lymphoma, or melanoma; squamous cell cancer from the head, lung or skin; a primary tumor of the sweat gland; or a neurogenic tumor (2,3). Biopsy of the axillary node usually can identify an extramammary site to help differentiate among these possibilities.
If the pathology of the axillary biopsy is consistent with breast cancer, the site of origin is usually one of the two breasts. Rarely, invasive breast cancer may arise in and replace breast tissue within axillary fat, be carcinoma from heterotopic breast tissue in a lymph node, or even be heterotopic glands in a lymph node, which may be misinterpreted as carcinoma (4).

When carcinoma is identified in the axillary node, a search of the ipsilateral breast is undertaken. This initially includes a clinical examination and a mamogram. If these are negative, an ultrasound, magnetic resonance imaging (MRI) or possibly even a positron emission tomography (PET) scan may be considered (3,5). A new breast primary may be found. Historically, when mastectomy and careful pathologic sectioning have been performed, a new breast primary has been located in 33–75% of cases (6–8). This report will present data on patients where no breast primary was found on the side with the axillary metastasis in order to highlight the complexity of this clinical scenario. Following the presentation of data is a discussion of the lymphatic drainage of the breast, known characteristics regarding CAM and suggestions for management.

MATERIALS AND METHODS

Between the years 1990 and 2004, at the New York Presbyterian Hospital–Weill Cornell Medical Center, seven women were identified who harbored CAM who had been treated for unilateral breast cancer. These were all validated by pathologic examination of the CAM revealing identical histologic and immunohistochemical features to the primary tumor in the opposite breast (Figs. 1 and 2).

The patients were evaluated for demographics, treatment modalities, tumor histopathology, recurrence, and outcome. Demographics included age at diagnosis, presence of a family history of breast cancer in first- or second-degree relatives and tumor location. Treatment characteristics included the type of surgical procedure and subsequent adjuvant therapy. Histopathologic characteristics of the tumor evaluated were cell type, overall size, presence of lymphovascular invasion, estrogen (ER), and progesterone (PgR) receptor status and HER-2/neu overexpression. The number of positive ipsilateral lymph nodes in relation to number of lymph nodes harvested was also documented. For the CAM, months to presentation, number of contralateral lymph nodes in relation to number of lymph nodes resected and presence of carcinoma in the contralateral breast were identified. Lastly, time from axillary presentation to follow-up as well as status at the last follow-up were recorded to determine outcome.

RESULTS

In this series of patients, the median age at diagnosis of the initial breast cancer was 49 years old (mean: 52, range: 35–65). Six of the seven (86%) women had a family history of breast cancer in at least one
first- or second-degree relative. In all women, the primary tumor was in the left breast. Anatomically, the tumor location varied: one was centrally located, one was in the lower inner quadrant, three were in the upper outer quadrant, and one was in the lower outer quadrant. The initial treatment consisted of lumpectomy followed by breast irradiation in six cases (86%) and modified radical mastectomy in the remaining one (14%).

At the time CAM was discovered, the breast contralateral to the original cancer was screened for a second primary. None of the patients had evidence of a new primary in the contralateral breast. One patient had a modified radical mastectomy of the breast contralateral to her original cancer; pathology revealed no disease in the specimen. Two patients had an MRI. Once could not identify any focal breast lesions and the second showed a 7 mm mass in the contralateral breast, which was consistent with a fibroadenoma upon biopsy. One woman underwent a planned, prophylactic mastectomy, which revealed no carcinoma in the specimen. Two patients had an MRI. One could not identify any focal breast lesions and the second showed a 7 mm mass in the contralateral breast, which was consistent with a fibroadenoma upon biopsy. One woman underwent a planned, prophylactic mastectomy, which revealed no carcinoma in the specimen. The remaining four patients had serial mammograms, which showed no evidence of cancer in the contralateral breast.

All seven patients had hormone receptor testing done on the original cancer, on any recurrences and on the CAM specimen. In these cases, the receptor status of the CAM specimen matched the original cancer. Regarding adjuvant treatment of the initial malignancy, all except one (14%) underwent postoperative radiation therapy (86%). Of the six women who had lumpectomies, all received breast radiation. The woman who had a mastectomy had postoperative chest-wall radiation also. This was recommended because of the presence of five positive axillary lymph nodes. Because of initial skin involvement, one woman had preoperative chemotherapy (14%) while five of seven (71%) women had postoperative chemotherapy. Two (29%) patients were placed on adjuvant tamoxifen. One (14%) patient underwent an autologous stem cell transplant because her pathology was interpreted as inflammatory carcinoma (Table 1).

Histopathologically, these were all infiltrating ductal carcinomas (100%), with an additional intraductal component in six (86%). The median tumor size was 1.1 cm (mean: 1, range: 0.8–3.5). Estrogen receptors were present in only two (29%) cases and no progesterone receptors were detected. In the four out of the five (80%) cases where the HER-2/neu status was evaluated, it was found to be overexpressed. Lymphovascular invasion of the primary tumor was identified in four of five (80%) cases. Only three of the seven (43%) women initially presented with positive ipsilateral lymph nodes. At the time of initial diagnosis, four (57%) patients had stage I disease and three (43%) were stage II (Table 2).

One (14%) of the patients had a synchronous presentation of the primary carcinoma and CAM. The remaining six (86%) had a median interval of 71 months (mean: 65, range: 24–96) between the primary cancer to CAM. When CAM was identified, the median number of positive nodes was 1 (mean: 2.6, range: 1–10). No cancer was found in the contralateral breast in any of these patients.

Regarding treatment of the CAM, one (14%) had surgical excision of the involved lymph nodes, five (71%) underwent a conventional axillary lymph node dissection and one (14%) had a needle biopsy of the lymph node only. For systemic adjuvant treatment all (100%) had chemotherapy, and one (14%) received hormonal therapy. With the treatment described, there were no axillary recurrences. The median duration of follow-up since the diagnosis of axillary disease was 35 months (mean: 37, range: 13–60). Three (43%) of the women were alive with disease, two (29%) were alive with no evidence of disease and two (29%) died of metastatic breast cancer (Table 3).

Table 1. Patient Demographics and Treatment Modalities

| Patient | Age at diagnosis | FH breast cancer | Laterality and initial tumor location | Surgical treatment of initial ipsilateral cancer | Adjuvant treatment of ipsilateral cancer |
|---------|-----------------|-----------------|-------------------------------------|-----------------------------------------------|----------------------------------------|
| 1       | 49              | Yes (sister)    | Left central                        | MRM                                           | Chemotherapy, radiation, stem cell transplant |
| 2       | 35              | Yes (maternal grandmother) | Left lower inner quadrant         | Lumpectomy                                    | Radiation, chemotherapy                  |
| 3       | 65              | Yes (daughter, paternal aunt) | Left upper outer quadrant         | Lumpectomy                                    | Radiation, chemotherapy                  |
| 4       | 48              | Yes (paternal aunt) | Left upper inner quadrant           | Lumpectomy                                    | Radiation, chemotherapy                  |
| 5       | 65              | No              | Left lower outer quadrant           | Lumpectomy                                    | Radiation, tamoxifen                      |
| 6       | 56              | Yes (maternal aunt) | Left upper outer quadrant           | Lumpectomy                                    | Radiation, tamoxifen                      |
| 7       | 43              | Yes (maternal great-aunt) | Left lower inner quadrant         | Lumpectomy                                    | Radiation, chemotherapy                  |
DISCUSSION

Lymphatic Drainage Pathways

In 1834, Sappey performed one of the earliest studies using injected mercury to trace the path of breast lymphatics. He demonstrated that the majority of breast tissue drains centrally into a subareolar plexus and then on to the axilla (9). By the mid-20th century, Turner-Warwick (10) showed that axillary lymph nodes receive approximately 75% of the lymphatic drainage from the ipsilateral breast and, also, that the ipsilateral internal mammary chain represents a significant alternative pathway of lymph drainage from both the lateral and medial halves of the breast. Drainage to the contralateral axilla is also possible and likely to occur via the subcutaneous lymphatics. Using various tracers, Haagensen (11) postulated that carcinoma reaches the nodes of the contralateral axilla via embolism or permeation through a deep lymphatic fascial plexus beneath the opposite breast. He theorized that tumor cells also traveled through collateral lymphatics, which cross the anterior chest wall from one axilla to the other.

As sentinel lymph node (SLN) biopsy technique becomes increasingly popular, physicians are demonstrating nonstandard draining pathways of radiolabeled tracer in the lymphatic drainage of the breast. Blue dye, used in the localization of the SLN can sometimes be seen traversing the subcutaneous lymphatics across the chest wall. (Figure 3) Also, the lymphoscintogram performed after the injection of radiotracer in the breast for the identification of the ipsilateral SLN will demonstrates a “hot” node in the opposite axilla, contralateral to where the isotope was injected (Figure 4). It has been shown that peritumoral or deep injection of dye or tracer is more likely to identify internal mammary nodes when compared to the more frequently used technique of subdermal

![Figure 3. Preoperative isosulfan blue dye injected into the left breast deep to the areola seen crossing the anatomic midline.](image-url)
injection which more commonly identifies axillary nodes (12).

Although the ipsilateral axilla is the predominant basin for drainage, any pattern of flow from any quadrant of the breast can occur. It is further hypothesized that when ipsilateral drainage is impaired by tumor, irradiation or previous axillary surgery, the normal channels are blocked and alternative drainage routes may be utilized (13). The two most likely routes of contralateral drainage are the deep fascial lymphatic plexus of the thoracic wall and the dermal lymphatics which cross the midline (1).

Prevalence and Characteristics of CAM

CAM probably occurs more frequently than it is reported. There are two reports in the literature which detail a similar series of patients with CAM. We compare our data to theirs to offer recommendations for treatment. In 1969, Devitt and Michalchuk published a series of 52 cases of CAM in a retrospective review of 1440 women with breast cancer over a 15 year period at the Ontario Cancer Foundation. The diagnosis was based on clinical presentation following treatment for a breast primary contralateral to the involved axilla. In 1998, Daoud and colleagues in Tunisia identified six cases of CAM among 123 women treated for primary operable breast cancer. Mammographic exam of the breast revealed no new primary tumor. The pathologic characteristics of the contralateral axillary nodes were identical to the original primary in all patients. The incidence of CAM in these two studies occurred in 3.5–5% of all breast cancers.

In our series, the patient and tumor characteristics demonstrated are indicative of more aggressive breast cancers based on age at diagnosis as well as histopathologic features. The median age of initial breast cancer diagnosis was 49 years of age, which is approximately 15 years younger than the average age at which the statistical majority of women develop breast cancer. Daoud’s group had a similar finding with a mean age of 48. Devitt’s study did not mention the age of the women. In our series 86% of women had a family history of breast cancer in a first or second degree relative. This is considerably higher than the commonly accepted 15% incidence of patients with breast cancer who have affected relatives. Also, at presentation, most primary cancers in this series were hormone receptor negative, HER2/neu overexpressing and had lymphovascular invasion. These are all known poor prognostic factors not present in the statistical majority of newly diagnosed breast cancers.

Among the seven women described in this series, all of the initial tumors arose in the left breast. However, they were located in all quadrants. Sizes ranged from sub-centimeter to over 3 cm, with none of the tumors being more than a T2. In comparison, five out of six of Daoud’s patients had T4 tumors and the remaining patient had a T3 primary with five out of the six primary tumors located in the central or inner aspect of the breast. It has been argued that the larger a tumor, the more likely it is to manifest contralateral spread. But, it is important to note that contralateral spread was identified even in smaller tumors examined in this series. Therefore, we did not demonstrate size to be a critical determinant of likelihood of CAM. Daoud also hypothesized that the closer a tumor is to the midline, the more likely crossing it becomes (1). Devitt, however, showed that the majority of primary tumors in his study were actually located in the outer quadrant (11). Our series is similar to Devitt’s and demonstrates that an inner quadrant location is not necessarily suggestive of CAM, reinforcing the difficulty in predicting CAM.

In the older studies, the methods of primary breast cancer treatment are not discussed. However, it can be assumed that all patients were treated according to the standard of care at the time of diagnosis. The primary breast cancers in our seven patients were treated with a combination of surgical excision, radiation, and chemotherapy. The decision to perform breast conservation therapy or mastectomy depended on the size of the tumor, its relationship to breast size, and patient preference. This was followed by radiation, chemotherapy, and/or hormonal therapy as indicated by tumor size, tumor grade or lymph node status.

Figure 4. Preoperative lymphoscintogram demonstrating isotope injected into the right breast with subsequent uptake in the left axilla.
Grouping the seven patients described here, as well as the 58 in Devitt's and Daoud's reviews, all but three developed the CAM following a combination of surgery, chemotherapy and/or radiation. In our series, only one woman presented with CAM at the time of her initial breast cancer diagnosis. The remaining six developed CAM between 2 and 8 years later. In Devitt's series, only two women presented with CAM at the time of initial breast cancer diagnosis, while 18 of the remaining 50 patients (36%) developed it as the first sign of recurrence of breast cancer. Of the remaining CAM in this series, five were detected at the time of a local recurrence, three at the time of distant metastases, fourteen following local recurrence and ten after distant metastasis. This supports the hypothesis presented earlier that when ipsilateral drainage is impaired by tumor, irradiation, or previous surgery, the normal channels are blocked and alternative drainage routes may occur.

In two women, the development of CAM reflected advancing systemic disease which resulted in breast cancer-related death. Amongst Devitt's patients, the development of CAM led to death in all but three cases, as a result of the associated systemic disease. According to Devitt's data, with higher presenting stages of cancer, the incidence of CAM was also higher: 2.3% in stage I, 3.9% in stage II, and 5.6% in stage III. Interestingly, all of our patients were stage I or II at CAM presentation. Lastly, Devitt found an inverse relationship between stage and median survival after presentation of CAM (14). With only seven patients in our series, we saw no survival difference based on the initial stage of the primary breast cancer.

What this Means for Treatment

Since the presence of a CAM is uncommon, treatment cannot be standardized. Even though the number of patients in this series is too small for statistical analysis, a key concept is that the treatment decision must be made individually on all available clinical and pathologic data. In addition to clinical exam, mammogram, and extent of disease workup, there are more sensitive tests currently available to detect an occult primary in the breast ipsilateral to the CAM. Clinicians may also use breast ultrasound or MRI, both of which provide additional information and may help to locate an occult primary. Ruling out a new primary is made more accurate with MRI (5). This was not available in our earlier cases, so the security of diagnosis is with long term follow-up and the absence of the appearance of new primary in the CAM breast. In addition, there was one patient who underwent a planned, prophylactic mastectomy which verified the absence of malignancy in the breast adjacent to the CAM.

In summary, if these tests fail to reveal a new primary cancer and there is no evidence of systemic metastatic disease, treatment for patients with a CAM needs to be individualized. The type of surgery may be a simple excision or an axillary dissection, whichever will provide adequate removal of the involved axillary lymph nodes. In this series, there were no axillary recurrences with the treatments described.

We have demonstrated that CAM may occur anatomically via a direct lymphatic route across the chest wall because the initial ipsilateral primary cancer treatment has interrupted the normal lymphatic drainage. This is still considered stage IV disease, so systemic therapy was utilized in all of our patients with the intent of possibly improving relapse-free survival.

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