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Presentation of Axillary Metastases from Occult Breast Carcinoma

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ABSTRACT
Axillary presentation from occult breast cancer is uncommon and continues to be a diagnostic and therapeutic challenge to physicians. Once the diagnosis of adenocarcinoma metastatic to an axillary lymph node has been confirmed, a preoperative workup should be done. The current experience is based on several relatively small retrospective reviews and case reports. It is difficult to determine the best management of occult breast cancer. However, treatment of axillary lymph node dissection is recommended for local control and complete staging information. Treatment of breast should be a choice between breast conservation with whole-breast radiotherapy and mastectomy. Adjuvant systemic treatment should be offered.

KEYWORDS: occult breast cancer, axillary metastases, mastectomy, breast conservation, radiotherapy.

Breast cancer presenting with malignant axillary metastases with no identifiable breast tumor is uncommon, and is typically referred to as occult breast cancer (OBC). It is classified by the American Joint Committee on Cancer (AJCC) as $T_0N_{1-2}M_0$ Stage II~III. Despite the fact that modern breast imaging techniques have significantly improved our ability to identify obscure, nonpalpable lesions, a small number of patients continue to present with OBC. It continues to be a diagnostic and therapeutic challenge to physicians.

Incidence

OBC was first recognized by Halsted in 1907[1]. He described three patients who had presented with axillary masses 1 to 2 years prior to a tumor becoming clinically evident in the breast. Two years later Cameron reported three more similar cases with axillary masses and no palpable tumor in the breast. He suggested that those axillary masses most likely represented metastatic breast carcinoma[2]. Thereafter many studies on OBC have been reported. OBC accounts for 0.3 to 1% of newly diagnosed breast carcinomas[3-8]. Baron and colleagues identified 35 patients (0.35%) who presented with a negative clinical examination and mammogram, and had metastatic axillary adenocarcinoma of an unknown primary site among 10,014 breast cancer patients between 1975 and 1988[4]. In another large review study, Foroudi and colleagues identified 20 patients (0.33%) with occult primary breast cancer among 6,047 patients treated between 1979 and 1996[6]. Shi

et al.[8] reported 33 patients (0.66%) with OBC among 4,986 breast cancer patients from 1953~1985. With extensive breast imaging, including ultrasonography and magnetic resonance imaging (MRI), micro lesions of breast cancer (T1mic or Tis) have been identified[9,10]. With increasing newer technology of breast imaging modalities, theoretically, the incidence of OBC will trend to decrease.

Presentation and Diagnosis

The clinical presentation of occult breast cancer is typically that of an axillary mass, discovered by the patient, which has persisted for several months[8]. In some of the patients the axillary mass may persist for years. The patients often have no other symptoms. The size of an axillary mass often is about 3 cm, but some of them are over 5 cm. The time to presentation of a primary breast tumor after axillary metastasis varies up from 0.5~5 years[11].

After a careful history and complete physical examination, the initial workup should include bilateral mammography, screening breast ultrasonography, and chest radiography (Fig.1). Most lymphadenopathy associated with any anatomic site has a benign etiology[12], and typically no treatment is necessary. The most common malignant etiology of persistent axillary adenopathy is lymphoma. In a review of 72 patients undergoing excisional biopsy for unilaterally enlarged axillary lymph nodes, 23.6% were found to be malignant (13.9% lymphoma, 9.7% metastatic carcinoma). In women, the most common primary tumor site was the breast. The nonbreast primary tumors were often diagnosed as lymphoma, melanoma and were rarely from the lung, ovaries, thyroid, gastrointestinal tract, liver, pancreas, or kidney[13].

If standard breast imaging studies reveal no suspicious lesion, excisional or needle biopsy of the axillary mass is very important and necessary. A definitive diagnosis of metastatic primary breast carcinoma with no suspicious lesion in a primary site can be difficult to make. However, detailed histologic studies such as hormone receptor and HER2/neu status, as well as histochemical stains by monoclonal antibodies M_4G_3 (MAb M_4G_3) against human breast cancer, can be helpful in supporting the diagnosis of a breast primary tumor[14,15]. Positive staining for estrogen and progesterone receptors are suggestive of a breast cancer origin, although other solid tumors, such as melanoma, renal cell carcinoma, and colorectal cancer, may also be estrogen-receptor positive[4]. Kaufmann et al.[14] found that the sensitivity and specificity of ER expression in breast carcinoma compared to other carcinomas were respectively 0.63 and 0.95, with lower values found for PR expression. An estrogen receptor–negative axillary mass does not rule out a breast primary tumor. The MAb M_4G_3 against human breast cancer is a glycoprotein with molecular weight of 56 kDa. The specificity of MAb M_4G_3 to breast cancer is over 90%, and the result of MAb M_4G_3 is correlated with the ER and PR result[15]. The combined detection of ER, PR and MAb M_4G_3 will help the diagnosis of OBC.

Mammography is still the most efficient method to detect breast lesions. Approximately 25% of the patients first thought to have an OBC ultimately are identified of their breast primary tumor by mammography[13]. Ultrasonography as an alternative imaging technique has been routinely used for detecting breast lesions. By this technique, Lee and colleagues identified two OBC cases that were confirmed by further biopsy[9]. Therefore any suspicious lesion on mammography or ultrasonography should be subjected to image-guide biopsy. MRI has high sensitivity in detecting and determining the extent of breast cancer and the information provided by this modality has proven valuable in patient management[16]. In several reports, MRI has shown to be highly efficient to assess occult breast cancer patients in whom conventional imaging has failed[10,17,18]. Orel et al.[17] identified the tumor correctly in 19 of 22 patients (86%) by MRI. The most common findings were spiculated or irregular focal masses ranging from 5 to 30 mm, with a mean of 17 mm. Olson and colleagues were able to identify the primary breast lesion using MRI in 28 of 40 (70%) women who had presented with adenocarcinoma metastatic to an axillary lymph node with no evidence of a breast primary tumor on physical examination or mammography[18]. MRI may provide evidence for a clinician and patient to make appropriate treatment decisions (ie, mastectomy vs breast conserving surgery vs whole breast radiotherapy).

Other innovational imaging modalities that may prove useful for the identification of occult breast cancers include positron emission tomography (PET) and nuclear medicine techniques[19,20]. Avril et al.[19] demonstrated that PET could be used to evaluate large axillary metastases in breast cancer patients with a 95% sensitivity and a 65% specificity. PET has been successfully used to identify hypermetabolic foci in mammographically occult breast cancer patients and may be a useful diagnostic tool in the management of patients with occult breast cancer

Clinical Management

The management of OBC is a persistent controversy.

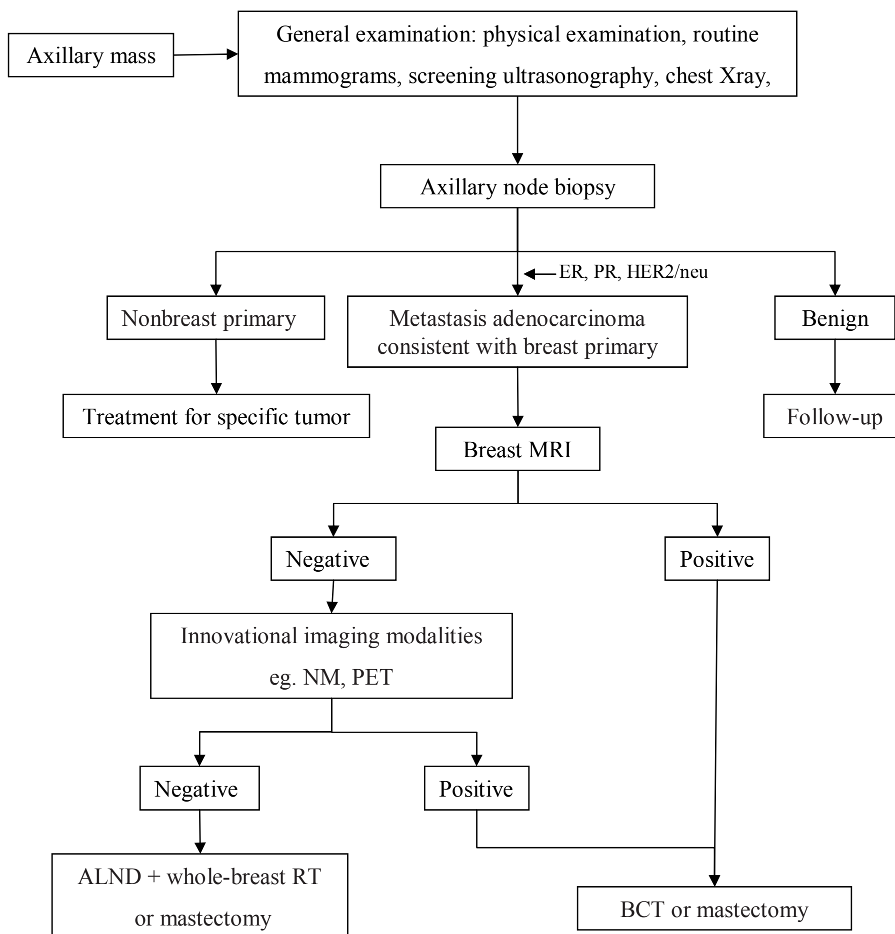

Fig.1. Algorithm for diagnosis of patients with axillary adenopathy. NM: Nuclear medicine studies. PET: Positron emission tomography. ALND: Axillary lymph node dissection. RT: Radiotherapy. BCT: Breast conservation.

Current experience is based on several relatively small retrospective reviews and case reports. It is difficult to compare and draw conclusions based on such studies owing to changes in treatment trends over time, lack of standardization, and limited follow-up.

Initially, mastectomy was the standard treatment for OBC, dating back to the description by Halsted. The advantage of mastectomy for OBC treatment is that it will confirm the diagnosis of OBC after detailed pathological examination. In a review of 10 published case series, Brenin discovered that a primary breast cancer was found in 61% (107 of 176) of patients after undergoing a mastectomy[13]. These reports were studied from 1946 to 1998. Only evaluation of the four most recent series among the 10 series reveals 18% (7/39) of patients identified their primary tumor. A dramatic reduction in the proportion of tumors identified in mastectomy specimens of patients could be explained by advances in breast imaging over the past 20 years. In addition, the size of a primary tumor may be too small to be identified by pathology findings. Recently a Japanese group reported a case of occult breast cancer with a size of 1.5×1 mm identified as an invasive ductal carcinoma by pathology[21]. The tumor size was smaller than the intervals at which the pathological sections (5 mm) were examined. Niu et al.[15] found primary breast cancer in 85% (44/52) of patients after mastectomy by serial sectioning of a total resected specimen at 5 mm intervals. In another study they also reported 84% (26/31) of identification of primary tumor in mastectomy specimens[22]. In 77% of the cases the size of the tumors found were less than 1 cm and the smallest size was only 2 mm.

The characteristics of OBC are comparable to patients with Stage II~III breast cancer, and the prognosis of patients with OBC is equivalent or slightly better than other patients with Stage II~III breast cancer. Breast conservation for the treatment (BCT)

of OBC would be a therapeutic option[23]. BCT consists of a lumpectomy and whole breast radiotherapy. Feigenberg et al. [24] first described a blind upper outer quadrantectomy, but they failed to produce a better outcome. In addition, Tench et al.[25] suggested that a significant number of cancers would be missed in a blind upper outer quadrantectomy. Thereby the blind upper outer quadrantectomy was dismissed as a justifiable alternative.

Several studies compared whole-breast radiotherapy with only-observation after axillary node biopsy and/or dissection as treatment for OBC. The identification of a breast tumor in patients receiving whole-breast radiotherapy was 12% to 33% whereas there were 14% to 83% in patients under observation[6,26,27]. Vlastos et al.[23] also reported a survival of 50% versus 83% between patients who were observed and those receiving radiotherapy. Thereby treatment to the primary site of cancer is very important. Comparison studies have been conducted on local treatment of OBC with mastectomy or whole breast radiotherapy. The studies demonstrated no statistically significant difference in survival[23,28]. However, in the majority of reports, the risk of local failure was higher than that typically reported for patients undergoing lumpectomy. The risk of local failure was higher but not excessive; therefore, the results of these studies strongly support the use of breast conservation, consisting of axillary lymph node dissection and whole-breast radiotherapy as an alternative to mastectomy for the treatment of patients with OBC.

Recent results from a survey of the American Society of Breast Surgeons on therapeutic options for OBC showed that 43% of respondents preferred “mastectomy” and 37% chose “whole breast radiotherapy[29]”. The rest of respondents were grouped as others which included “observation”, “patient choice” “PET examination”and “non-contributable”. It was obvious that a small majority of physicians still prefer mastectomy although recent literature supported the use of whole breast radiotherapy[11,29]. The appropriate treatment of the breast after an axillary presentation of OBC continues to be a controversial issue.

Adjuvant treatment for OBC, including adjuvant chemotherapy and adjuvant hormonal therapy, is siminar for the therapy for Stage II or III breast cancers. Neoadjuvant systemic therapy should be considered for patients who present with N2 disease to allow tumor down-staging prior to an axillary dissection. The role of adjuvant radiotherapy to the axilla and chest wall for patients who have undergone modified radical mastectomy should be determined by the number of metastatic lymph nodes.

Prognosis

The prognosis of women with OBC presenting with axillary metastases appears to be equivalent to, or slightly better, than that of stage-matched patients with preoperatively detectable primary breast tumors[3,6,30,31]. The prognostic factors for patients with OBC presenting with axillary metastases were related to the number of metastases involving axillary lymph nodes, presenting of involved supraclavicular lymph nodes and distant metastases[32]. Studies have shown better overall survival in estrogen receptor–positive tumors[4] and with no relationship between the size of the primary tumor and distant metastases-free survival[33].

Summary

OBC is an uncommon tumor, and its best management is difficult to determine and remains controversial. In general, once the diagnosis of adenocarcinoma metastatic to an axillary lymph node has been confirmed, an extensive preoperative workup should be done. Breast imaging studies should consist of bilateral mammography, screening ultrasonography, and breast MRI. Treatment of axillary lymph nodes dissection is recommended for local control and complete staging information. Treatment of the breast should be a choice between breast conservation with whole-breast radiotherapy and mastectomy, since survival is equivalent. Adjuvant systemic treatment should be offered.

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