

Occult Primary Breast Cancer Presenting With Axillary Nodal Metastasis: Report of 3 Cases

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Abstract

Occult primary breast cancer presenting as axillary metastasis is a very rare entity of breast cancer. Diagnosis and treatment management represent a real challenge in the absence of consensual attitude.

We report 3 cases of occult breast cancer who presented with metastatic nodule in the axilla. Although histology identified a metastatic adenocarcinoma in the lymph nodes, mammography failed to detect the primary tumor. Immunohistochemistry showed that the biopsied lymph nodes were positive for both estrogen and progesterone receptors in all cases, suggesting the breast as the site of the primary tumor. Breast MRI was normal in addition to thoraco-abdomino-pelvic scan. Axillary dissection was performed with breast conservation followed by ipsilateral breast radiotherapy, then adjuvant chemotherapy. They are currently being treated with tamoxifen without evidence of disease with a median follow up of 8 months.

Keywords: Cancer; Breast; Occult; Axillary dissection; Radiotherapy; Chemotherapy; Hormone therapy

Introduction

Occult primary breast cancer presenting as axillary metastasis is very rare, accounting for less than 1% of all breast

cancers. It is defined as carcinoma that has metastasized to the axilla in the absence of mammographic or physical findings of disease in the breast.

Axillary metastasis without an obvious primary tumor remains a difficult diagnostic and therapeutic challenge.

Cases Presentation

We report 3 cases of occult breast cancer revealed by axillary metastasis, collected in department of medical oncology at Hassan II University Hospital over a period of 5 years from January 2007 to January 2012. All patients had clinically axillary lymph node without breast lesion on physical examination or on mammography. Biopsy of axillary nodes was performed and showed at the immunohistochemical analysis a metastatic process positive for estrogen and progesterone receptors and negative for Her2. Breast MRI was normal in all cases in addition to thoraco-abdomino-pelvic scan. All patients underwent axillary dissection with breast conservation. Histological analysis of axillary dissection showed more than 3 lymph node metastases in all cases. Then they received ipsilateral breast radiotherapy. The three patients received sequential adjuvant chemotherapy (anthracycline - taxane) followed by hormone therapy. Evolution was marked by good control after a median follow up of 8 months. Patients were also very satisfied by esthetic result (Table 1).

Discussion

Breast cancer presenting as axillary adenopathy with clinically occult breast tumour was first described by Halsted in 1907 [1]. Reported series suggest that 0.3-1% of early breast cancers present with axillary metastases in the absence of a breast primary on clinical examination or mammography.

Malignant neoplasms of other organs known to metastasize to the axillary nodes include melanomas and carcinomas of lung, thyroid, stomach, colon, rectum, pancreas and ovaries. However, these metastases are rarely the first signs of disease. Since occult primary breast cancer is a rare con-

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Table 1. Diagnostic and therapeutic characteristics of patients

	Cas No. 1	Cas No. 2	Cas No. 3
Age	54	45	57
Axillary node	Left	Right	Left
Mammography	Normal	Normal	Normal
Breast MRI	Normal	Normal	Normal
TAP scan	Normal	Normal	Normal
Immunohistochemistry	ER: 50% RP: 70% Her2 negative	ER: 20% RP: 5% Her2 negative	ER: 10% RP: 60% Her2 negative
Surgery	Axillary dissection	Axillary dissection	Axillary dissection
Pathology	7 N (+)	5 N (+)	8 N (+)
Radiotherapy	Ipsilateral breast radiation	Ipsilateral breast radiation	Ipsilateral breast radiation
Medical treatment	*Sequential chemotherapy *Hormone therapy	*Sequential chemotherapy *Hormone therapy	*Sequential chemotherapy *Hormone therapy
Evolution	Good control	Good control	Good control

dition, its management is unlikely ever to be determined by randomized trials. With the use of breast MRI and modern imaging modalities, its incidence is likely to reduce even further with time [2].

Where mastectomy is performed in such patients, a primary breast cancer is found in 45-82% patients [3-5]. However, where the breast primary is occult following breast MRI in addition to clinical examination, mammogram and ultrasound, the frequency of detection of breast primary in mastectomy specimen is lower (20-33%) [6, 7].

Magnetic resonance imaging has a high sensitivity for the detection of breast cancer, ranging from 88 to 100%. Reports have documented an identification rate of 70 to 86% of occult primary tumors in the breast with contrast-enhanced MRI. The technique is not without its limitations and still has a percentage of false-positive and scarce false-negative results. The magnitude of breast density does not seem to limit the efficacy of breast MRI. In fact, MRI may reveal occult lesions even in breast tissue that appears mildly dense mammographically. In this case, false-negative breast Magnetic Resonance Imaging (MRI) failed to identify a 12 mm invasive ductal cancer. Although rare, one limitation of breast MRI is that the lack of vascular enhancement of a neoplasm may lead to an inability to differentiate the tumor from surrounding breast parenchyma [6, 8].

As for all carcinomas of unknown primary site, a staging by CT scans of thorax, abdomen and pelvic must be performed to exclude another primary site or other eventual

metastasis [9]. Positron Emission Tomography (PET) has been successfully used in the detection of occult breast carcinoma and holds promise in the diagnosis of the primary tumor in these challenging cases, particularly in women with radiodense breasts. There is also evidence that breast scintimammography may be a useful, inexpensive and practical diagnostic tool in the evaluation of the patient with occult breast cancer, but experience with this modality is still limited [10, 11].

A fine-needle aspiration biopsy or core biopsy can be performed as the initial diagnostic test. A negative result does not exclude a malignancy and, therefore, an excisional biopsy may be necessary.

Positive results of oestrogen and progesterone are suggestive of breast cancer, and this occurs in approximately 50% of females. However, negative ER/PR staining does not exclude the diagnosis of breast cancer and it is important not to forget that other carcinomas (cancer of the colon, ovary, endometrium, kidney and melanoma) may show detectable ER/PR expression. Kaufmann et al. studied the possibility of differentiating metastatic breast carcinomas from other metastatic adenocarcinomas immunohistochemically. They reported that the sensitivity and specificity of ER expression in breast carcinoma compared with all other carcinomas were 0.63 and 0.95, respectively, with lower values found for PR expression. They also reported the usefulness of gross cystic disease fluid protein 15 (GCDFP-15; also known as BRST-2), which is a marker of apocrine differentiation. The

sensitivity and specificity of GCDFP-15 expression were 0.98 and 0.62, respectively. In addition, the combination of GCDFP-15 and/or ER or PR had a sensitivity of 0.83 and a specificity of 0.93 for carcinomas of the breast [12].

The mammaglobin antibody is another sensitive marker of breast carcinomas. Bhargava et al. recently reported that the sensitivity of mammaglobin is better than that of GCDFP-15, but it lacks the specificity of GCDFP-15. Mammaglobin expression is not altered at the metastatic lymph node site and can help, in combination with other markers, to establish the correct diagnosis of metastatic breast carcinoma [13].

Regarding treatment, there is no clear consensus concerning optimal treatment of occult breast cancer. Patients with axillary metastases consistent with breast carcinoma should be treated identically to those with the same features and a proven primary breast neoplasm.

The traditional therapy of choice was radical or modified radical mastectomy. However, several recent studies have shown no statistically significant differences in outcome between mastectomy and more conservative treatments, such as limited resection and/or radiation [3, 14]. These findings suggest that breast-conserving therapy is an option for the treatment of occult breast cancer. This clinical entity has been managed differently by observation, upper outer quadrantectomy, radiotherapy to the breast and mastectomy [15]. Data from larger studies eventually revealed an unacceptable outcome in patients, who only had a “wait and see” therapeutic approach. A blind upper outer quadrantectomy was first described by Feigenberg et al. but these efforts failed to lead to a better outcome. Arguments can be made both for and against whole breast radiation and mastectomy.

Literature does not clearly support the overwhelming use of one or the other. However, with whole breast radiation, the breast is preserved and the survival rates would surely support its use as an alternative to mastectomy.

To assess the role of ipsilateral breast radiotherapy (IBR), 55 patients were included between 1975 and 2009 at The Royal Marsden Hospital and Institute of Cancer Research [16].

48/55 patients had no detectable breast primary after magnetic resonance imaging (MRI) in addition to other imaging. 35/48 patients (73%) were treated with radiotherapy to the conserved breast, and 13/48 (27%) with observation. Patients who had IBR had better 5 year local recurrence free survival (84% versus 34%, $p < 0.001$), and relapse free survival (64% versus 34%, $p = 0.05$), but no difference in overall survival (OS) (84% versus 85%, $p = 0.2$). There was no difference in 5 year LRFS (80% versus 90%: $p = 0.3$) between patients who received radiation of 50 Gy in 25 fractions versus ≥ 60 Gy.

For our patients, the attitude was the breast conservation with axillary dissection, followed by ipsilateral breast radiotherapy. For medical treatment, patients were treated identi-

cally to those with the same features with proven primary breast neoplasm. They received adjuvant chemotherapy with anthracycline and taxane, then hormone therapy.

Conclusion

Occult primary breast cancer with axillary metastases is a very rare entity. Treatment remains very controversial and must be in a multidisciplinary approach. Axillary dissection with breast conservation and ipsilateral breast radiotherapy seems to be a good therapeutic option and can be recommended to improve local control in addition to esthetic results.

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