

# Failure of imaging techniques in revealing breast cancer progression

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## Summary

This study focuses on a case of a 67-year-old woman with occult breast cancer involving the axillary lymph nodes. The instrumental examinations employed, positron emission tomography included, were not useful in diagnosing the disease. When the patient was surgically treated micro-invasive breast cancer was diagnosed. This peculiar malignant pathology is a matter of discussion especially because it is hardly diagnosable. Because of such diagnostic difficulties it may happen that micro-invasive carcinoma progression can easily mislead routine diagnostic screenings performed on women over 50.

**Key words:** Breast cancer; Micro-invasive breast carcinoma; Early diagnosis; Imaging techniques.

## Introduction

In 1907 Halstead [1] first described two patients with invasive carcinomatosis and axillary involvement derived from hidden breast carcinoma, which became evident after some months in both patients. According to the Armed Forces Institute of Pathology (AIP) [2], micro-invasive breast carcinoma (MIBC) is a rare lesion occurring in less than 1% of cases with breast cancer, which poses a peculiar diagnostic problem. The definition of ductal micro-invasive carcinoma has been the subject of several revisions. A number of terms have been coined: foci of stromal invasion [3], i.e. microscopic foci of malignant cells invading beyond the basement membrane [4], and one or two minute foci of invasion [5] in addition to quantitative criteria ranging from < 1 mm [6-8] to < 5 mm of invasion [9, 10]. Other authors have associated micro-invasive carcinoma to different lesions grouped under the term of "minimal breast carcinoma", including carcinoma in situ [11] and carcinomas with invasion up to 5 mm [10, 12] or 1 cm [13, 14]. In the last few revisions of the TNM classification system, MIBC is defined as the extension of malignant cells beyond the basement membrane into the adjacent tissue with no focus more than 0.1 cm [15].

Involvement of the axillary lymph nodes may be the first sign of occult breast carcinoma, as in the cases described by Halstead. In the experience of Kyokane *et al.* [16], when axillary lymph nodes were involved, occult breast cancer affected 19 of 62 patients. On the other hand, other authors report cases of lymph node involvement with primary lesions which were not identified even after surgery [17-19]. These early-metastasizing MIBCs (emMIBC) pose both diagnostic and therapeutic problems.

We report a case of a patient with emMIBC in which several imaging techniques did not allow the detection of either the primary lesion or early metastases involving the axillary lymph nodes.

## Case report

D.S., a 67-year-old Caucasian woman, underwent yearly postmenopausal gynecological screening up to the onset of her disease. In February 2001, on the occasion of the last screening, an enlarged right axillary lymph node 13 mm in size was detected at echography. Instead, the mammogram did not reveal pathological alterations. A month later, the lymph node was resected and the histology was positive for carcinoma. Due to the lymph node site and gland-like structure, and being immunohistochemically positive for cytokeratines, metastatic breast adenocarcinoma was diagnosed.

In May 2001 the patient was examined for the first time at our oncological center. With respect to the documentation and in accordance with some authors, mastectomy was recommended. However, the patient rejected this surgical treatment and opted for routine screenings. In June, she underwent echography demonstrating for the second time the presence of an enlarged lymph node which was again resected and the histology resulted to be similar to the previous one. Following the above-mentioned surgical treatment, neither mammography nor positron emission tomography (PET) detected any pathology. Finally in August, the patient underwent mastectomy and homolateral lymphadenectomy. The definitive histological examination revealed in the resected breast parenchyma an area with a diameter of 4 mm affected by carcinoma in situ, infiltrating in some points with metastases in three out of the 23 resected lymph nodes (pT1a, N1 biii, Mx). The tumor grading was 2. The hormonal receptors resulted intensively positive for estrogens and moderately positive for progesterone on the primary lesion but negative on the tissue affected by metastases. The proliferation index, assessed through immunoreactivity to Ki 67, was 3% on the primary lesion while it was 25% on the tissue affected by metastases. C-erb-B2 was negative both on the primary lesion and on the tissue affected by metastases. Following surgical treatment, the patient received adjuvant therapy

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with four administrations of doxorubicin, 75 mg/m<sup>2</sup> every 21 days followed by six cycles of CMF (cyclophosphamide 600 mg/sqm, methotrexate 40 mg/m<sup>2</sup> and 5-FU 600 mg/m<sup>2</sup> every 21 days) and by radiotherapy (total dose 5000cGy). Later on, the patient underwent hormone therapy with tamoxifen 20 mg/d. Presently, after 27 months of follow-up, the patient is disease-free.

## Conclusions

It is common knowledge that MIBC is a clinical entity which is hardly detectable. Mammography, which is also able to reveal unpalpable lesions affecting the breast, has a sensitivity ratio ranging from 75% to 95% and a specificity ratio ranging from 89.4% to 99.1% [20-24]. Sensitivity and specificity ratios are higher in women aged 50 and older, although the sensitivity ratio decreases and the specificity ratio increases in the following examinations compared to the first few screenings [20-24]. In order to have MIBC properly diagnosed, a biopsy of the lesions is indispensable, and can be done due to the recent introduction of the mamotome [25] and upright and prone stereotactic mammography [26, 27]. As far as magnetic resonance (MR) is concerned, the way the pathological areas are displayed using this technique also needs some tissutal morphological changes of a certain entity [28].

The problem becomes serious when MIBCs are subject to early metastases. Comedocarcinoma is the most frequent histological subtype of ductal carcinoma in situ (DCIS) and is associated with micro-invasions with percentages ranging from 66.7% to 80% of cases with micro-invasions [6, 29-33], followed by papillary types of DCIS with percentages ranging from 6.2% to 18.4% of micro-invasive forms [2, 6, 30, 31, 33]. Instead, we do not have sufficient knowledge of the molecular features associated with the specific behavior of early metastasizing cancers. In the case described here for example, although the differences between primary metastatic lesions clearly indicate that metastasis is a phenomena of phenotypic selection, the small starting focus was not particularly aggressive: relatively differentiated tumor, positive hormonal receptors, low kinetic cells. Attitudes to metastasis are better studied through other parameters such as cathepsin D, laminin receptors, plasminogen activators and inhibitors as well as tumor angiogenesis [34-42]. However, the way our case evolved demonstrates that recommending radical surgery following detection of the first metastatic lymph node was correct. Also chemotherapy and radiotherapy following surgery resulted to be appropriate for high-risk breast cancer (5 axillary lymph nodes involved in all) in accordance with several authors [43-48] stating that the MIBC needs to be treated as a clinically detectable carcinoma.

Some clinical histories show that all diagnostic tests are unable to detect an emMIBC which is spreading locoregionally. In our case two mammograms and one PET proved to be useless. In particular, the PET was performed only some weeks before the surgical treatment which demonstrated the involvement of three axillary lymph nodes. This in spite of the fact that PET is con-

sidered a non invasive alternative to the sentinel lymph node methodology for those patients who may be candidates for treatments without lymph node surgical dissection of the axillary arch [49-52].

In conclusion, whenever a patient's clinical history poses some doubts, a PET and MR of the axilla should be performed along with mammography and, if necessary, mamotome. Still, unfortunately, emMIBC may escape the most accurate breast cancer screening procedures and the patient, as in our case, may turn up when the cancer is in a progressive stage.

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