



# Axillary metastases from occult breast cancer.

## Our experience



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### Axillary metastases from occult breast cancer. Our experience

We report the case of a 63-year-old woman with occult breast cancer who presented with a hard metastatic nodule in the left axilla. Although histology identified a metastatic carcinoma in the lymph nodes, numerous tests failed to detect the primary tumor. Resected lymph node was positive for both estrogen and progesterone receptors, suggesting the breast as the site of the primary tumor. Left modified radical mastectomy was performed. Pathology revealed an invasive lobular carcinoma (2.5 x 2mm in size) with extensive lymphatic involvement, which strongly expressed both vascular endothelial growth factor-C (VEGF-C) and VEGF-D.

KEY WORDS: Occult breast carcinoma, Axillary metastases, Hormone receptors, Vascular endothelial, Growth factors

### Introduction

Women presenting with metastatic carcinoma in the axillary lymph nodes pose a challenging diagnostic and therapeutic problem, especially when the metastasis is the sole clinical symptom of disease. Although the breast is the most likely site for the primary tumor, non-palpable breast cancer presenting as an axillary metastasis (that is, occult breast cancer) is rare. Here we report a

case of occult breast cancer that was diagnosed using immune-histochemical markers identified in the resected axillary lymph node metastasis, and was treated by modified radical mastectomy. We also investigated the immune-histochemical status of two members of the vascular endothelial growth factor (VEGF) family, VEGF-C and -D, which have been associated with lymph-node metastases.

### Case report

A 63 year-old woman presented at our clinic in November 2012, complaining of a hard nodule (2.5 cm in size) in the left axilla. There was no palpable mass in the left breast, no nipple discharge and no sign of infection in the left arm. Chest computed tomography (CT) revealed that the left axillary lesion was made up of two oval masses (2.5 x 1.0 and 2.0 x 1.5 cm in size).

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There were no abnormal findings in the lungs. Serum levels of carcinoembryonic antigen (CEA) and soluble interleukin-2 receptor (sIL-2R) were within normal ranges. Serum antibody tests to detect toxoplasma and cytomegalovirus were negative. Excisional biopsy of the shallower mass was performed under local anesthesia to confirm the diagnosis. Histological examination identified metastatic carcinoma in one lymph node.

Breast cancer was initially considered as the primary focus. However, no signs of abnormality were found in the breast using mammography, ultrasonography or magnetic resonance imaging (MRI). Therefore, to identify the origin of the metastasis, the patient underwent further tests including ultrasonography and CT of the neck, abdomen, and pelvis, gastrointestinal endoscopy, and colonoscopy. Serum levels of carbohydrate antigen 15-3 (CA15-3), carbohydrate antigen 19-9 (CA 19-9), cancer antigen 125 (CA 125), and alpha-fetoprotein (AFP) were within normal ranges. Despite these extensive investigations, no primary tumor was detected. However, immune-staining of the resected lymph node for both the estrogen receptor (ER) and the progesterone receptor (PR) produced positive results. Based on these findings, we concluded that the axillary lymph node metastasis was caused by occult breast cancer. A modified radical mastectomy of the left breast was therefore performed in January 2013, after obtaining informed consent from the patient. Serial sections at 5 mm intervals were prepared from the resected specimen and, unexpectedly, revealed an invasive ductal carcinoma (1.5 x 1 mm in size), with extensive involvement of the lymphatics, in the upper outer quadrant of the breast. Immunostaining for hormone receptors showed that over 75% of carcinoma cells were positive for the ER, but less than 10% of them were positive for the PR. Only one of the fifteen resected lymph nodes contained a carcinoma, which had been observed preoperatively as an axillary mass on the CT scan. The patient recovered well after surgery and is presently being treated with anastrozole.

We also investigated the expression of VEGF-C and -D immune-histochemically in the metastatic lymph node. The results showed that carcinoma cells, which were positive for cytokeratin, also stained with affinity-purified goat polyclonal antibodies against VEGF-C and -D.

## Discussion

Carcinomas of the lung, thyroid, stomach, colon, rectum, and pancreas have the potential to spread to the axillary lymph nodes; however, these metastases are rarely the first manifestations of disease. Non-palpable breast cancer presenting as axillary metastases is also rare, accounting for less than 0.5% of all breast cancers<sup>1,3</sup>. However, in such cases it is important to consider occult breast cancer during the early stages; a correct diagnosis

of breast cancer with axillary metastasis at stage II can be treated immediately by radical mastectomy, whereas widespread metastases are incurable by stage IV. It is therefore difficult to decide on how extensively an investigation should be performed in order to exclude other possible origins of the metastasis. Although we performed CT scans and endoscopy in this case, positron-emission tomography might be particularly useful in searching for the primary cancer in similar cases. Immune-histochemical markers have proven useful for differentiating metastatic breast carcinoma from adenocarcinoma arising in other primary sites. Positive results from staining resected axillary lymph nodes for ERs and PRs are suggestive of breast cancer. Kaufmann et al.<sup>4</sup> 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. Han et al.<sup>5</sup> reported that mammaglobin expression in the lymph nodes was an important marker of metastatic breast carcinoma, with a sensitivity of 0.84 and a specificity of 0.85 for breast carcinomas, as assessed by immunohistochemistry. The treatment of occult breast cancer remains controversial. 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<sup>1,6</sup>. In the present case, our patient chose a modified radical mastectomy and a 2.5-mm primary breast cancer was detected in serial sections of the total resected specimen, which were taken at 5-mm intervals. There was a strong possibility that this primary cancer would not have been detected, because the tumor size was smaller than the intervals at which the pathological sections were taken. Other studies have reported that primary breast tumors could not be identified in approximately 30% of specimens from patients undergoing mastectomy for occult carcinoma<sup>2,3,7</sup>. In such cases, the primary tumors in the breast may be too small to be detected by conventional pathological assessment.

Although, in this case, the primary tumor was found in the lower inner quadrant of the breast, nearly one-half of all detectable primary occult breast tumors are located in the upper outer quadrant, and 20% are located in the lower outer quadrant<sup>2,8</sup>. This suggests that the outer half of the breast is the most likely location for

such primary tumors. Occult breast cancer has a high metastatic potential to the regional lymph nodes, despite the relatively small tumor size. VEGF-C and -D secreted by tumors have been associated with tumor lympho-angiogenesis. These growth factors can bind to VEGF receptors on lymphatic endothelial cells, and induce the proliferation and growth of new lymphatic capillaries, which has been reported to increase the incidence of regional lymph node metastasis. Kurebayashi et al.<sup>9</sup> investigated mRNA expression of VEGFs in breast tumors. They found that although VEGF-A and -B were expressed in both node-positive and node-negative tumors, VEGF-C expression was detected in nine out of 12 node-positive tumors (75%) and in zero out of eight node-negative tumors (0%). Another immune-histochemical study identified VEGF-D expression in 86 out of 105 cases (81.9%) and found that VEGF-D labeling was significantly correlated with lymph node metastasis (p 1/4 0:0238).<sup>10</sup> Ishikawa et al.<sup>11</sup> reported that lymph node metastasis was significantly related to the expression of VEGF-C and -D in early histologically undifferentiated gastric cancers. We found that the cytokeratin-positive carcinoma cells in lymph-node metastasis also expressed VEGF-C and -D. We therefore suggest that these growth factors could play an important role in the diagnosis of occult breast cancer.

## Conclusion

Occult primary breast cancer with axillary metastases is a very rare entity. Treatment remains very controversial and must be in a multidisciplinary approach. 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<sup>3,12</sup>. This clinical entity has been managed differently by observation, upper outer quadrantectomy, radiotherapy to the breast and mastectomy; 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<sup>13</sup>. 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.

## Riassunto

Riportiamo il caso di metastasi ascellare sinistra da carcinoma occulto della mammella in donna di 63 anni. Nonostante la FNAC deponesse per metastasi da carcinoma, nessun accertamento pre operatorio è riuscito a determinarne la provenienza. L'istologia del linfonodo asportato, ha dimostrato la presenza di recettori per gli estrogeni ed il progesterone nel tessuto metastatico. Sottoposta a mastectomia radicale modificata sinistra, l'accurato esame del pezzo operatorio ha rivelato la presenza di carcinoma lobulare infiltrante (2,5 x 2 mm) con ampio coinvolgimento linfatico e con sopra espressione del fattore di crescita endoteliale vascolare (VEGF-C e VEGF-D).

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