Medullary Thyroid Carcinoma Metastatic to Breast Masquerading as Infiltrating Lobular Carcinoma*

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ABSTRACT

Metastatic tumors to the breast from an extramammary site are rare entities and may present diagnostic difficulties for the surgical pathologist because of frequent histological similarities to primary neoplasms in this location. A case is reported of medullary thyroid carcinoma metastatic to the breast in a 28-year-old woman with a family history of MEN IIA (Sipple's) syndrome. Histological features resembled infiltrating lobular carcinoma and included the so-called “targetoid” and “Indian file” patterns. Immunostaining revealed the true nature of the lesion and was diffusely positive for calcitonin, chromogranin, and carcinoembryonic antigen. Electron microscopy disclosed typical neurosecretory granules confirming the diagnosis. A brief review of the literature and differential diagnosis is also presented.

Introduction

Metastatic tumors to the breast account for 0.8% to 6.6% of all breast malignancies.1,2 In almost one-third of the cases, the metastatic focus represents the initial clinical presentation of an occult primary, usually a carcinoma,3 although more frequently it is a sign of widespread dissemination of the tumor.1 Metastatic carcinoma from the opposite breast is the commonest secondary tumor to the breast in females as opposed to hematopoietic tumors (lymphomas and leukemias) and prostate carcinoma which are the commonest metastatic tumors to the male breast.1,2,4 In addition to these, metastatic disease has been associated with malignant melanoma,1,5,6,7,8 lung carcinoma (oat cell type in particular),1,6,8,9 renal cell carcinoma, gastrointestinal carcinoma,5,6 thyroid (papillary and follicular carcinomas),6,10 carcinoids,11,12,13,14 ovarian carcinoma,3,5,8,15 endometrial carcinoma, pancreatic carcinoma,5 as well as hepatoma and neuroblastoma.8 In children rhabdomyosarcoma,16 medullo-
blastoma and glioblastoma\textsuperscript{17,18} have been reported. A case of metastatic medullary thyroid carcinoma to the breast diagnosed in fine needle aspirate has been reported,\textsuperscript{19} to our knowledge, the current study is the first report of medullary thyroid carcinoma metastatic to the breast with a description of histological, immunohistochemical, and ultrastructural features.

**Case Report**

A 28-year-old female was admitted to North Shore University Hospital for the evaluation and treatment of a right breast lump which was noted by her a few weeks prior to admission. Past medical history was significant for a diagnosis of MEN IIA (Sipple's) syndrome and for multiple surgical procedures. In January, 1988, she presented with a thyroid lump and underwent a total thyroidectomy for a multifocal and bilateral medullary thyroid carcinoma with positive right paratracheal lymph nodes. Her postoperative calcitonin dropped but never reached normal limits, and a month later she was readmitted for a palpable node in the right neck. She underwent a right modified neck dissection with metastatic medullary carcinoma in nine regional lymph nodes. Again her postoperative calcitonin levels remained elevated, and she was readmitted six months later. Although no nodes were felt at this time, she underwent an elective left modified neck dissection again with positive lymph nodes. Her calcitonin level returned to normal postoperatively. Family history was significant for MEN IIA syndrome in the patient’s father, sister, and daughter.

During the current admission in June, 1993, a sonogram of the breast showed a well-circumscribed lesion thought to be a fibroadenoma vs breast carcinoma. She underwent a lumpectomy with removal of a 1 cm nodular mass. Frozen section showed a carcinoma with an infiltrating pattern. Pertinent laboratory findings at that time included a mildly elevated calcitonin level. She had an uneventful postoperative recovery.

**Materials and Methods**

**Light Microscopy**

Specimen was fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned at 4 microns, and stained with hematoxylin and eosin.

**Immunohistochemistry**

Sections were cut at 3 microns, deparaffinized in xylene, rehydrated and quenched in methanol with 4% hydrogen peroxide for twenty minutes. Slides were incubated with primary antibody overnight at 4°C. Labelled avidin biotin method was used, and immunostaining was demonstrated with diaminobenzidine-hydrogen peroxide reaction and counterstained with Gill’s III hematoxylin. All antibodies were used with appropriate controls.

**Electron Microscopy**

Formalin-fixed paraffin embedded tumor, in the breast, was rehydrated, post fixed in buffered 1% osmium tetroxide, buffered with 0.1 M cacodylate (pH 7.3), stained en bloc with uranyl acetate, dehydrated in a graded series of ethanol, and embedded in effapoxy resin. One micron plastic sections were stained with toluidine blue. Thin sections were stained with uranyl acetate and lead citrate and examined on a JOEL JEM 100 CXII electron microscope.

**Results**

**Morphologic and Immunohistochemical Findings**

Grossly, the specimen was a tan-grey nodule, well circumscribed with a smooth pale white cut surface, and a maximum diameter of 1 cm. Light microscopic studies showed a well circumscribed tumor with a histologic pattern resembling infiltrating lobular carcinoma. The predominant feature was the typical “targetoid” or “bull’s eye” arrangement of small to intermediate
sized uniform cells with hyperchromatic nuclei and scanty amount of amphophilic cytoplasm. This pattern was characterized by the formation of the concentric rings around residual mammary ducts (figure 1).

In addition, the classical pattern of individual malignant cells arranged in single files or so called “Indian file” with intervening strands of thick collagenous stroma was also seen in areas (figure 2). Also noted were areas in which tumor cells formed distinct lobular structures as well as more solid nodules. No organoid architecture was noted, and none of the residual mammary ducts or lobules showed an in situ component. Spindle cells and extracellular amorphous material resembling amyloid were also absent from the lesion, and congo red stain was negative. Immunohistochemical studies were done (figure 3) and are summarized in table I.

Sections from the thyroidectomy specimen with the primary medullary carcinoma were reviewed and showed a variegated histological pattern consisting predominantly of nests of uniform angulated or spindly cells (figure 4) admixed with round or oval cells within a delicate fibrovascular stroma which, in places, contained masses of homogeneous eosinophilic material which was strongly congophilic, consistent with amyloid deposits. Multifocal capsular and vascular invasion were present.

ULTRASTRUCTURAL FINDINGS

By electron microscopy, the cytoplasm of the tumor cells contained variable numbers of relatively small, round, dense core granules (figure 5). There was also a well developed, rough endoplasmic reticulum, clusters of intermediate filaments, and lysosomes.
FIGURE 2. Medullary thyroid carcinoma metastatic to breast. Collagenous mammary stroma with columns of tumor cells forming 'Indian files' (hemotoxylin & eosin ×200).

FIGURE 3. Medullary thyroid carcinoma metastatic to breast. Tumor cells with strong immunostaining for calcitonin. A mammary duct with negative staining is seen at the top of the picture (calcitonin ×200).
# TABLE I
Summary of Immunohistochemical Findings

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Source</th>
<th>Dilution</th>
<th>Staining Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitonin</td>
<td>Dako, Carpinteria, CA</td>
<td>1:2,000</td>
<td>+++</td>
</tr>
<tr>
<td>CEA (monoclonal)</td>
<td>Biogenex, San Ramon, CA</td>
<td>Prediluted</td>
<td>++</td>
</tr>
<tr>
<td>Chromogranin</td>
<td>Boehringer–Mannheim, IN</td>
<td>1:10,000</td>
<td>+++</td>
</tr>
</tbody>
</table>

CEA = carcinoembryonic antigen.

## Discussion

Metastatic tumors to the breast present perplexing diagnostic problems both from the clinical as well as histological points of view. Accurate diagnosis of metastatic lesions is important to avoid unnecessary, radical surgical procedures and to assure appropriate adjunctive therapy.\(^1,14\) There are no reliable clinical criteria for distinguishing a primary tumor from a secondary tumor in the breast. However, a superficial, sharply circumscribed solitary mass when noted in the upper-outer quadrant, especially if attached to the overlying skin, or multinodular masses in the superficial tissues of the breast should raise the question of a metastatic lesion.\(^1,2,14\) Mammography may show nodular lesions with diffuse

![Figure 4. Medullary thyroid carcinoma. Primary tumor showing nests of uniform spindly cells with multiple amyloid deposits in the stroma (hemotoxylin & eosin ×100).](image)
thickening of the skin\textsuperscript{15} and absence of spiculations or microcalcification.\textsuperscript{3} Histological features which may be suggestive of metastatic disease include a periductal or perilobular distribution in the absence of any \textit{in situ} ductal or lobular component. There is minimal elastosis and desmoplasia associated with these lesions.\textsuperscript{4} Final confirmation usually requires immunohistochemical and ultrastructural studies to establish the diagnosis of metastasis.

Fine needle aspiration biopsy can also play an important role in identifying a suspected metastatic neoplasm in the breast. Especially when combined with immunocytochemistry, the sensitivity and diagnostic capability of this process is further enhanced and is extremely useful in differentiating secondary malignancies of the organ.\textsuperscript{8,19}

The current case report exemplifies some of these difficulties because of the histologic similarity of the metastatic medullary thyroid carcinoma to a primary infiltrating lobular carcinoma of the breast, owing to a prominent periductal and perilobular distribution of the neoplastic cells. When faced with such a situation at the time of intraoperative consultation, it is prudent to defer the final diagnosis, awaiting the results of immunohistochemical or ultrastructural studies. The need for good communication between the surgeon and the surgical pathologist in these cases cannot be over-emphasized.

Most of the metastatic tumors in breast have been described in younger or middle-aged women, perhaps because the better blood supply in this age group encourages blood-borne metastasis, the most frequent mode of cancer spread to this organ.\textsuperscript{9} Overall prognosis of these cases is usually grave with approximately 90\% of the patients dying within a year.\textsuperscript{1,2,15}

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References