Case Report:

Invasive mammary carcinoma with neuroendocrine differentiation: a diagnostic challenge

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Abstract:

Neuroendocrine differentiation has been reported in both in situ and infiltrating breast cancers. The prognostic significance of neuroendocrine differentiation in mammary carcinoma is unclear. The spectrum ranges from undifferentiated small cell carcinoma to ductal carcinoma in situ with neuroendocrine differentiation. Mucinous carcinomas of the breast appear to have the greatest association with neuroendocrine differentiation. We add to the literature a case of a morphologically composite mammary infiltrating ductal carcinoma with diffuse neuroendocrine differentiation as demonstrated by immunohistochemical staining. We reported a case of 76 year old female diagnosed as infiltrating ductal carcinoma in which there was a morphologically conventional-appearing infiltrating ductal component admixed with nests of cells that resembled a carcinoid tumor and initially mimicked the appearance of intraductal carcinoma. Immunohistochemical stains for synaptophysin and chromogranin demonstrated diffuse, strong positivity uniformly throughout the tumor, even in the more conventional-appearing areas. We concluded that this was an infiltrating ductal carcinoma with morphologic and immunohistochemical evidence of neuroendocrine differentiation. The presence of neuroendocrine differentiation in a morphologically composite tumor should be reported but that the tumor should essentially be classified according to existing schemes of ductal and lobular carcinomas and variants. There is no evidence that neuroendocrine differentiation is prognostically significant.

Keywords: Breast neoplasm; Neuroendocrine tumor

Introduction

Neuroendocrine differentiation of breast is a rare tumor. They arise from cells able to produce peptide and amines referred to as diffuse neuroendocrine system. The significance of neuroendocrine differentiation in carcinomas of the breast remains unclear. The spectrum ranges from undifferentiated small cell carcinoma to ductal carcinoma in situ with neuroendocrine differentiation. Mucinous carcinomas of the breast appear to have the greatest association with neuroendocrine differentiation. It is likely that neuroendocrine mammary carcinomas derive from progressive neuroendocrine differentiation in a subset of cancerous cells rather than from pre-existent endocrine cells. Neuroendocrine differentiation can be found in different histotypes of breast carcinoma, including in situ and invasive ductal, lobular, colloid, papillary breast cancer. Clayton et al. detected the presence of argyrophilic and dense granules by electron microscopy in different histotypes of mammary breast cancer.
Case report
A 76-year-old woman with no significant medical history was found to have a palpable left breast mass in the upper outer quadrant. A fine-needle aspiration cytology was performed. Smears showed highly necrotic ductal carcinoma. No cytologic features of neuroendocrine differentiation were noted either initially or upon review. Then patient underwent modified radical mastectomy, specimed measured 15x15x6cm. On serial sectioning a growth measuring 2x1.5 cm was identified. Cut surface was greyish white. Tumor was 0.2cm away from resected base grossly. Representative microsections examined showed infiltrating ductal carcinoma breast with neuroendocrine differentiation. Focal areas of mucin production was also seen. Overlying skin, nipple and areola were free from tumor infiltration. Resected base showed infiltration by tumor. Lymph nodes isolated (8) showed reactive hyperplasia.

Special stains for the neuroendocrine markers synaptophysin, chromogranin and neuro specific enolase were performed and showed diffuse positivity in both the nests and in the more conventional invasive ductal carcinoma. Morphologically transitional areas were also strongly and diffusely positive for synaptophysin and chromogranin. Positive and negative controls were appropriate. Adjacent non-neoplastic breast was negative.ion. Additional tests performed included estrogen, progesterone, and HER-2/neu receptor staining. The tumor was positive for estrogen receptors and progesterone and HER-2/neu receptors. Modified radical mastectomy was performed.

Discussion
Neoplasms with neuroendocrine differentiation do not constitute a specific histopathological category of female mammary carcinoma, but it is apparent that there is a group of mammary carcinomas capable of producing ectopic hormonal substances. The recognition of these features is necessary for defining their clinical characteristics. 4 Multiple studies have been undertaken to identify a pre-existing population of neuroendocrine cells in breast tissue. An early study demonstrated the presence of chromogranin-reactive endocrine cells in normal breast tissue as well as in so-called argyrophilic or carcinoid tumors of the breast. Other studies demonstrated dense-core granules by electron microscopy. 1 Pure carcinoid tumors of the breast have been reported, as have small cell carcinomas and composite tumors (ie, tumors with more conventional-appearing types of breast carcinomas admixed with or coexpressing neuroendocrine carcinoma morphologically or immunohistochemically).

Among composite tumors, the mucinous carcinoma is the type most commonly associated with neuroendocrine differentiation. 1 Neuroendocrine (NE) was not recognized as a single entity until the last WHO’s classification. This classification differentiates between four different subtypes: (i) small-cell carcinoma (SCC); (ii) large-cell carcinoma; (iii) solid NE carcinoma; and (iv) atypical carcinoid tumor. For simplification, this section describes the solid neuroendocrine subtype (SN) which represents a better prognosis group. (The SCC subtype is described in the ‘poor prognosis, ER positive’ section.) 5

Histologically the neuroendocrine component resembles lung and gastrointestinal neuroendocrine tumors. It is characterized by cellular monotony, nuclear palisading, pseudorosette formation, loss of cell cohesion, and abundant eosinophilic cytoplasm and nuclei with stippled (‘salt and pepper’) chromatin. Nevertheless these features per se are not
sensitive enough to rule in a diagnosis because they are inconsistently present. A panel of the most sensitive and specific IHC neuroendocrine markers (chromogranin A or B and synaptophysin) are known.\textsuperscript{6}

Main reported morphological features in neuroendocrine breast cancer are:
- production of mucin, retained into the cells or secreted in extracellular milieu;
- presence of insular structures separated by fibrovascular stroma;
- low nuclear grade and granulous cytosol.

There are no specific clinical features associated with mammary carcinomas that exhibit structural or histochemical evidence of endocrine differentiation, so most of the lesions are palpable tumors or can be detected by imaging.\textsuperscript{2}

Histological grade is one of the most important parameter in disease clinical development. High grade neuroendocrine carcinomas show high proliferation rate and poor prognosis. Low grade neuroendocrine carcinomas with low proliferation rate are be consider to have a better prognosis. Another prognostic parameter is co-expression of neuroendocrine and non-neuroendocrine proteins such as glycoproteins and apocrine proteins. This capability is present in well differentiated mammary breast carcinomas while poor differentiated carcinomas don’t show it.\textsuperscript{2}

Sapino et al. has shown that mucin producing carcinomas and pure apocrine carcinomas have a better prognosis with a 5 years overall survival longer than poor differentiated neuroendocrine carcinomas.\textsuperscript{8}

Finally ER expression is an important prognostic parameter in neuroendocrine breast carcinoma and correlates to a long survival.\textsuperscript{2}

Differential diagnosis should include direct invasion of the breast by Merkel cell carcinoma, malignant lymphoma (either primary or as a manifestation of systemic disease), carcinoid tumor, and malignant melanoma, which should be excluded by the exact location and extension of the tumor and by immunohistochemical stains, such as leukocyte common antigen, neuroendocrine markers, S100 protein, and HMB-45, respectively. Modified radical mastectomy with axillary lymph node dissection seems to be the treatment of choice, with adjuvant radiation, chemotherapy, or both, based on the clinical stage and presence of metastasis.\textsuperscript{7}

**Conclusion**

The presence of neuroendocrine differentiation in a morphologically composite tumor should be reported but that the tumor should essentially be classified according to existing schemes of ductal and lobular carcinomas and variants.
References


