



## CASE REPORT

# Metaplastic carcinoma of the breast with neuroglial differentiation

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## KEYWORDS

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**Summary** We present a case of a 34-year-old female who had a rapidly enlarging right breast mass. Biopsy results were consistent with a neuroblastic neoplasm of the breast. Neoadjuvant chemotherapy for a neuroblastoma was performed followed by a modified radical mastectomy was performed. Final pathology revealed small foci of poorly differentiated carcinoma randomly distributed within extensive areas of neuroglial differentiation. Such a lesion has not been described in the current literature to our knowledge, and we propose that this neoplasm is a metaplastic carcinoma with a novel heterogeneous differentiation. Subsequent therapy consisted of standard adjuvant breast cancer chemotherapy and radiation therapy.

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## Introduction

Metaplastic carcinoma of the breast is an uncommon finding, thought to represent less than 1% of all breast cancers.<sup>1-3</sup> They are a heterogeneous group of invasive breast cancers where a variable portion of the epithelial component has undergone transformation. They are typically divided into two categories those with squamous differentiation and those with heterologous elements. Many types of

tissue have been reported, but to date neuroglial differentiation has not been reported.<sup>4</sup>

## Case report

### Clinical presentation

A 34-year-old female presented with increasing firmness and fullness of the right breast. The patient was nursing her third child age 17 months at the time and was felt to have developed mastitis

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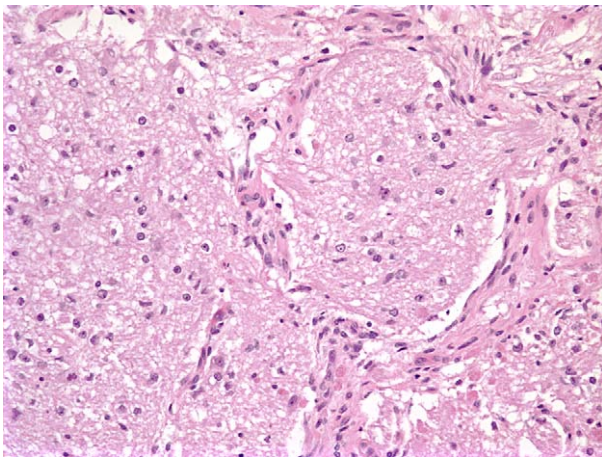
with a possible abscess. She was treated with several courses of antibiotics without resolution.

### Initial pathologic investigation

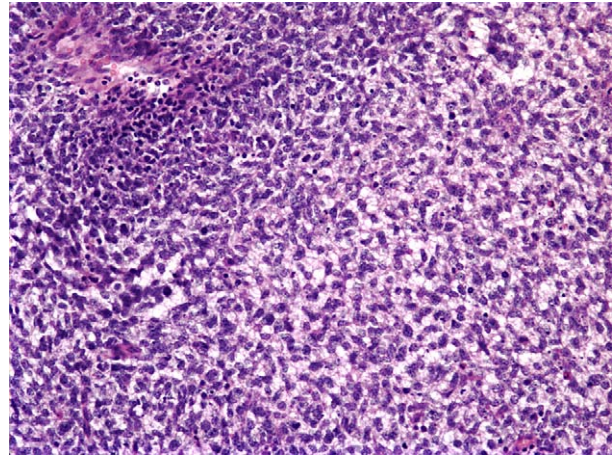
Eventually a fine needle aspiration was performed and cytology revealed a poorly differentiated carcinoma with neural differentiation. She then underwent a right breast needle core biopsy and right axillary node biopsy of a palpable node measuring 5 cm. Her pathology revealed a high-grade undifferentiated small blue cell neoplasm with neural differentiation (Figs. 1 and 2). No epithelial component was seen. Other pathology reviews from the outside referred to this a high-grade neuroblastic neoplasm. At presentation to our institution, she had her entire right breast replaced by tumor measuring 12 cm in greatest dimension. A pre-chemotherapy PET/CT revealed a large right breast neoplasm with uptake in two internal mammary lymph nodes, no other evidence of metastatic disease by body PET and CT scan. A bone scan did not reveal evidence of metastatic disease.

### Initial treatment

Her case was discussed by the pediatric oncology, breast oncology, breast surgical oncology and pathology services. Based on the pathology obtained, many features resembled a pediatric neuroblastoma and it was felt that treatment on a pediatric neuroblastoma protocol of VP-16 and cisplatin (EP) would be the best choice. After neoadjuvant chemotherapy she had a minimal response with softening of the tumor and its greatest dimension reduced to 10 cm.



**Figure 1** H&E Staining showing neural differentiation.



**Figure 2** High grade undifferentiated small blue cell neoplasm.

### Surgery

She underwent a right modified radical mastectomy and was discharged home the next day. Pathology revealed a 10.1 cm metaplastic carcinoma with epithelial and neuroglial differentiation metastatic to 5 of 9 additional lymph nodes. Occasional cells stained positive for progesterone receptor (PR) and gross cystic disease fluid protein (GCDFFP) supporting a breast origin. The tumor was estrogen receptor (ER) and Her2Neu negative.

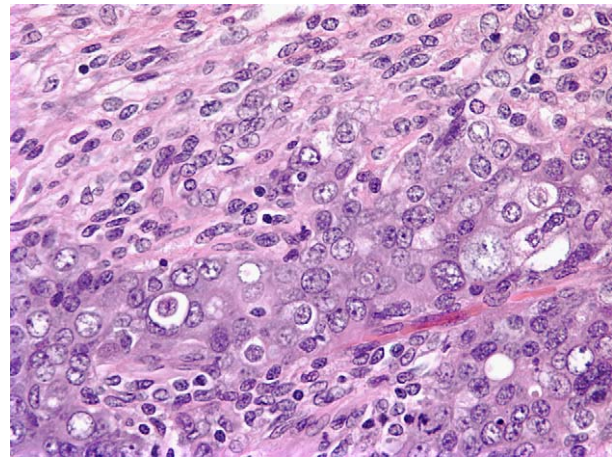
With the change in diagnosis to a metaplastic carcinoma she underwent treatment with dose dense Adriamycin/Cytosan followed by Taxol. Comprehensive chest wall, axillary, supraclavicular and internal mammary radiation will follow. Because of the rare positivity for PR, she will undergo 5 additional years of tamoxifen therapy.

The needle core biopsy and axillary lymph node removed before the start of chemotherapy contained two histological components. One component consisted of small blue cells with hyperchromatic nuclei and a high mitotic rate. These cells had an undifferentiated, or blastemic, appearance. This cell population merged into a second component that consisted of predominantly neuropil with larger neuronal and glial appearing cells.

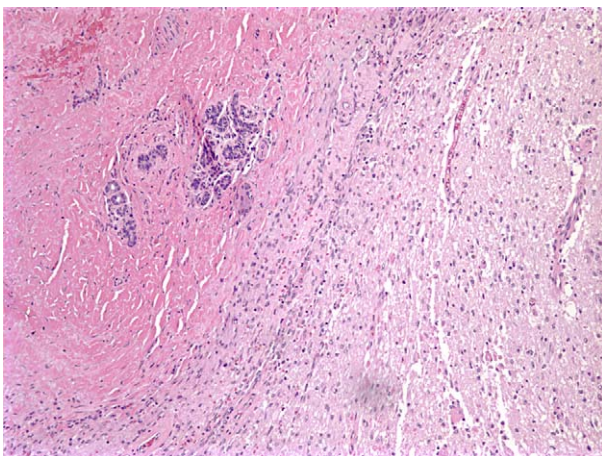
Sectioning of the mastectomy revealed a solitary, unencapsulated, ovoid 10.1 cm mass, with a tan, soft cut surface (Fig. 3). The tumor was predominantly solid, with focal cystic spaces measuring up to 1 cm. These cystic spaces were filled with blood and necrotic debris. The tumor came within 0.5 cm of the deep margin, and nine lymph nodes measuring up to 1.5 cm was found in the axillary tail. An additional deep margin including skeletal muscle removal revealed no additional tumor.



**Figure 3** Modified Radical Mastectomy specimen.



**Figure 5** Malignant epithelial cells.



**Figure 4** Mature neuroglial tissue and breast parenchyma interface.

Grossly, the tumor appeared well circumscribed, with compression of the surrounding residual breast tissue. Microscopic examination, however, revealed infiltration of the tumor through adipose tissue and extensive entrapment of benign breast epithelium.

Approximately 90% of the tumor volume consisted of mature neuroglial tissue (Fig. 4). The neuroglial areas consisted of an eosinophilic fibrillary matrix and cells with oval to round nuclei, small to inconspicuous nucleoli, and indistinct cytoplasm. Immunohistochemical studies supported the neuroglial phenotype, with strong diffuse staining for glial fibrillary acidic protein (GFAP), neurofilament protein, neuron specific enolase, S-100, and synaptophysin.

A total of 5–10% of the neoplasm consisted of scattered clusters of pleomorphic, cytologically malignant epithelial cells, not seen in the original incisional biopsy (Fig. 5). These cells contained coarse chromatin, multiple prominent nucleoli, and

moderate amounts of amphophilic cytoplasm. Atypical mitotic figures and tumor necrosis with cavitation were present. Several clusters contained poorly formed lumens. These areas stained strongly and diffusely for cytokeratin AE1/3 and focally for GCDFP, PR, p63, CD30, and CD99.

A single cluster was characterized by cytologically malignant nuclei with scant cytoplasm present, resembling a small round blue cell tumor. No rosettes were identified. Immunohistochemical studies could not further delineate the phenotype of these cells, as the cells disappeared on deeper sectioning.

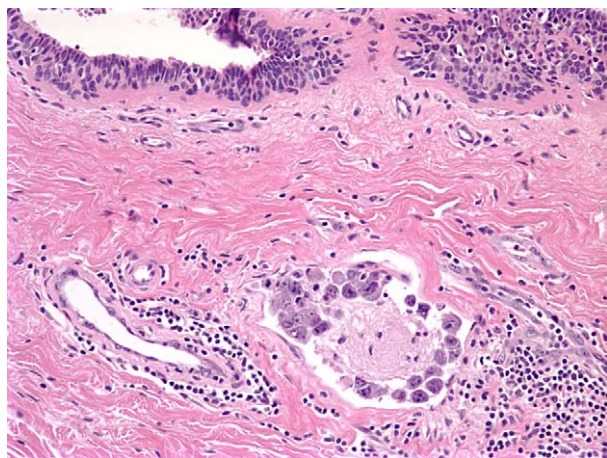
Small numbers of rhaboid cells were also identified; however, these cells were positive for neuronal markers. These cells probably represent chemotherapeutic effects, with engorged lysosomes causing the abundant eccentric eosinophilic cytoplasm. These cells were not present in the original biopsy material.

Subjacent to the nipple were two foci of lymphatic invasion. Both the malignant epithelial and glial components were present in the lymphatics (Fig. 6). Three lymph nodes were positive for scattered subcapsular malignant epithelial cells, and two lymph nodes contained confluent areas of mature neuroglial tissue.

While benign epithelium was present within and surrounding the tumor, no areas of atypical hyperplasia, in situ carcinoma, or conventional invasive breast carcinoma were identified.

Additional immunohistochemical stains for  $\alpha$ -fetoprotein (AFP),  $\beta$ -hCG, hepatocyte paraffin 1 (HepPar 1), carcinoembryonic antigen (pCEA), and chromogranin were negative.

Cytogenetics was performed on the tumor and showed a karyotype of 46, XX, t(6;18) (p21–22;q11) seen in all of the metaphases counted.



**Figure 6** Lymphovascular invasion with malignant epithelial and glial components.

## Discussion

We could not find any similar cases reported in the literature, and struggled for a long time on how best to classify it. Multiple opinions have been rendered regarding this tumor.

The initial biopsy material contained a prominent small round blue cell component, and a mature neuronal component. No epithelioid areas were present. This suggested the diagnosis of a neuroblastoma, which is characterized by neuroblastic cells with variable amounts of neuropil and Schwannian stroma. Immunophenotyping, however, did not support this diagnosis. While the tumor did stain for neuronal markers, it also stained for cytokeratins and CD99, both of which should not be present in a neuroblastoma.

The diagnosis of a primitive neuroectodermal tumor (PNET) was also suggested. PNETs have been reported to occur on the chest wall, and can stain positively for cytokeratins and CD99. Intercellular neuropil, however, is not a feature of PNET, and no rosettes were identified.

Other small round blue cell tumors suggested at the time of the incisional biopsy included rhabdomyosarcoma and hepatoblastoma. However, stains for desmin, myf4, AFP, and HepPar were all negative.

The diagnosis of an immature teratoma was considered. Teratomas should be composed elements derived from at least two germ layers. However, this case only demonstrated ectodermal differentiation.

The possibility of metastasis was also considered, but several features argued against this. Examination of the patient, including full radiologic surveys did not reveal evidence of distant disease. The pattern of lymph node involvement with extra-

mammary disease limited to regional lymph nodes is also consistent with a breast origin. The malignant epithelial cells stained positively for GCDFP, a marker of apocrine differentiation. GCDFP is highly specific marker for breast carcinoma when salivary gland and skin adnexal carcinomas have been ruled out.<sup>5</sup> Finally karyotyping was performed to see if the tumor could be a metastasis from the patient's male child. The XX karyotype of the tumor cells grown in culture ruled out this possibility, and the t(6; 18) translocation seen is not known to be characteristic of any particular type of tumor. Also, since the translocation was seen in all cells analyzed it may represent a constitutional rearrangement, rather than a tumor specific change.

The mastectomy specimen contained a prominent epithelioid component not seen in the original biopsy. These areas stained strongly for cytokeratins, and also stained for the breast markers GCDFP and PR. The presence of this epithelial component raised the diagnosis of metaplastic carcinoma. Metaplastic carcinoma of the breast is an invasive carcinoma in which the epithelial elements give rise to, and are often overshadowed by, nonepithelial elements. The nonepithelial elements typically include spindle cells (hence the alternate name "sarcomatoid carcinoma"), cartilage and bone. The epithelial component may consist of glandular or squamous elements, but is often highly inconspicuous, and the diagnosis rests of finding a few scattered cytokeratin-positive spindle cells. Other immunohistochemical results that were consistent with this diagnosis were positivity for p63 and CD99. It has been shown that metaplastic carcinoma is probably derived not from epithelial, but from myoepithelial derivation.<sup>5</sup> Additionally, CD99 has been shown to be positive in metaplastic carcinomas of the breast.

The standard of care for this carcinoma has traditionally been surgical with a modified radical mastectomy. The margins were clear of disease and comprehensive chest wall, axillary, supraclavicular and internal mammary node radiation was recommended do to its rapid onset of growth, large size and lymph node involvement.<sup>6</sup> Most cases of metaplastic carcinoma do not present with lymph node metastasis, however, the aggressive presentation of this case warranted radical local and adjuvant intervention. Most previous series of metaplastic carcinomas have found a large primary tumor at diagnosis like in our report.<sup>7,8</sup> Most cases do not express hormone receptors with estrogen and progesterone, ours weakly expressed progesterone.<sup>4,7,8</sup> Patients with metaplastic carcinomas tend to have poor outcomes with a high risk of recurrence after surgery and its systemic

management has rarely been reported in the small reviews to date.<sup>9</sup>

In conclusion, this appears to be a unique case which does not resemble anything in the current literature. While many types of tissue have been described in the nonepithelial component in the past, we believe that this case represents the first metaplastic carcinoma reported showing neuroglial differentiation.

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