

Breast Carcinoma Metastasizes to Brain-Three Unique Cases

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Citation

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Abstract

Metastatic breast carcinoma to the brain is a relatively common occurrence in patients with breast cancer. Brain metastasis is usually the later sequela for breast cancer patients. Mucinous carcinoma and metaplastic carcinoma are rare subtypes of breast cancers. Mucinous carcinoma has favorable prognosis and rarely develops brain metastasis. It is rare that initial presentation of a patient with neurological manifestation leads to the diagnosis of breast cancer. We report three unique cases of brain metastasis of breast carcinoma. 1) Mucinous carcinoma: A 52-year-old female had mucinous carcinoma in both breasts and been free of disease for 8 years. 2) Metaplastic breast carcinoma with an epithelial component with squamous and neuroendocrine differentiation and a mesenchymal component composed of chondroid differentiation: A 41-year-old female was diagnosed with metaplastic carcinoma eleven months ago. 3) Triple negative (negative for estrogen receptor, progesterone receptor and human epidermal growth factor receptor-2) breast carcinoma metastasis to brain as the initial presentation in a 71-year-old female. For less aggressive subtypes of invasive breast carcinomas such as mucinous carcinoma, brain metastasis can occur after many years of remission. For more aggressive subtypes of invasive breast carcinomas such as metaplastic carcinoma or triple negative invasive ductal carcinoma, brain metastasis can occur in the early phase of disease and rarely before the diagnosis of primary breast cancer.

INTRODUCTION

Approximately 15-40% of patients with known primary malignant neoplasms will present with brain metastasis.¹ Of all patients with brain metastasis there can be upwards of 15% of these patients with undiagnosed primary.¹ Breast cancer is the second most common metastatic tumor to the brain. Approximately 10-20% of breast cancers develop brain metastasis with increasing trend, which usually represent a late event for the patients.²⁻⁶

Mucinous carcinoma (colloid carcinoma) is a rare subtype of breast carcinomas, accounting for approximately 2% of all breast carcinomas. It uncommonly develops nodal metastasis and has a favorable prognosis.⁷⁻⁹ It is extremely rare that breast mucinous carcinoma metastasizes to the brain.

Metaplastic carcinoma is a rare tumor, accounting for less than 1% of invasive mammary carcinomas. It is referred to a heterogeneous group of tumors and is divided into purely epithelial and mixed epithelial-mesenchymal tumors. The latter will be called as carcinosarcomas when the mesenchymal component is malignant.^{10,11} Chondroid,

osteoid, or rhabdoid differentiation is the most common mesenchymal component.

The presence of metastatic breast cancer to the brain as initial presentation of breast cancer is very rare in the medical literature. Search of PubMed database yielded no reports of intra-parenchymal brain metastasis as initial presentation of breast cancer. However, we did find one case report of cavernous sinus syndrome and two reports of bilateral choroidal metastases to the eye as initial presentation of breast cancer.¹²⁻¹⁴

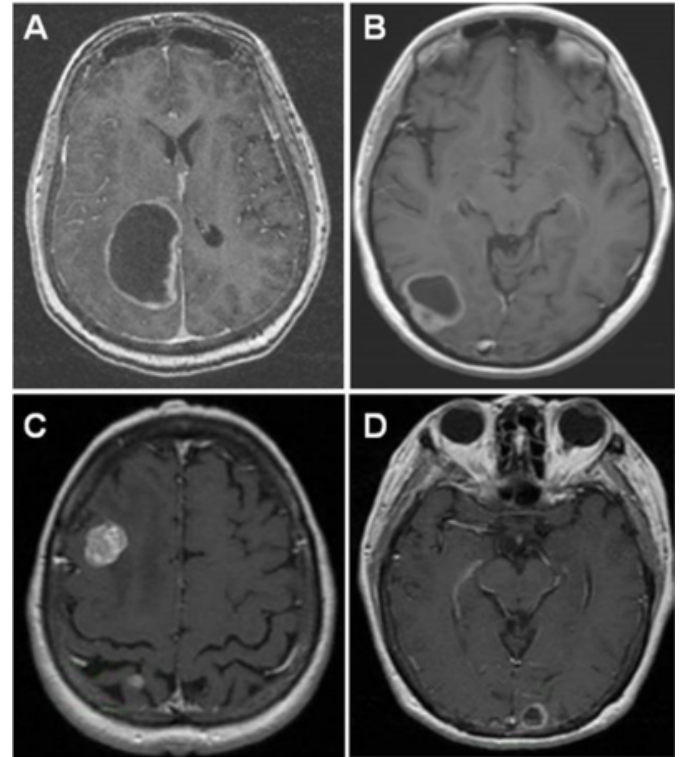
In this paper, we present three unique cases of brain metastasis of breast carcinoma. 1) Mucinous carcinoma. 2) Metaplastic breast carcinoma with an epithelial component and a mesenchymal component. 3) Triple negative breast carcinoma [negative for estrogen receptor (ER), progesterone receptor (PR) or human epidermal growth factor receptor-2 (HER2)] metastasis to brain as the initial presentation.

CASE REPORT

Case 1. A 52-year-old female presented with a lump in the right breast. The biopsy and mastectomy specimens showed mucinous carcinoma (Colloid carcinoma). Seven out of 32 right axillary lymph nodes were positive for metastatic carcinoma. Carcinoma cells were positive for Estrogen receptor (ER) (80%) and progesterone receptor (PR) (50%), but negative for HER-2/Neu. After 6 months, the mastectomy of left breast also showed mucinous carcinoma with 4 positive left axillary lymph nodes. After local radiation therapy, chemotherapy, and remaining disease free for eight years, she developed mild ataxia, and left-sided weakness and numbness. Brain MRI showed a large predominantly T2 hyperintense right parietal parasagittal peripherally enhancing lesion measuring approximately 4.7 x 3.8 x 5.8 cm with vasogenic brain edema (Fig. 1A). There was mass effect on the right lateral ventricle and 8 mm right-to-left midline shift. The findings were suspicious of metastatic tumor. Gross total resection of tumor was achieved. The intra-operative cytologic preparation and frozen section demonstrated classic metastatic mucinous adenocarcinoma, characterized by islands of bland looking epithelial cells in mucinous pools. Immunohistochemical studies showed carcinoma cells are positive for CK7, ER and PR (Fig. 2). The immunostain result for HER-2/Neu was equivocal (score 2+) and subsequent HER-2/Neu FISH revealed no amplification. The morphological and immunostain profiles were consistent with metastatic breast mucinous adenocarcinoma. CT and nuclear whole body bone scan did not show any other metastatic disease.

Figure 1

Axial, T1-weighted post-contrast administration.



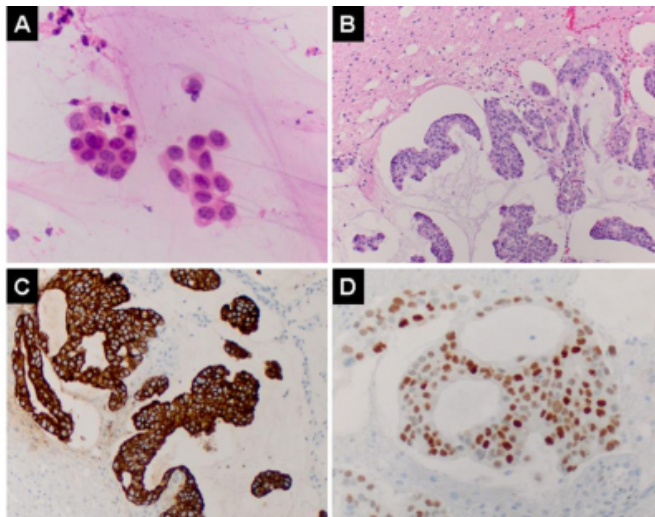
Case 1. A: A 4.7 x 3.8 x 5.8 cm right parietal parasagittal peripherally enhancing lesion.

Case 2. B: A ring-enhancing mass in the right occipital region measuring 3.1 x 2.7 x 2.0 cm.

Case 3. C and D: Three metastatic lesions: a 2.2 x 2.1 cm right frontal lesion, a 1.1 x 1.2 cm left occipital lesion, and a 6 mm posterior right frontal lesion.

Figure 2

Cytologic preparation shows small clusters of bland epithelial cells in a mucinous background. Hematoxylin and eosin (H&E) stain. X600. Metastatic mucinous carcinoma in the brain. H&E. X200. Metastatic mucinous carcinoma is strongly immunopositive for CK7. X200. Metastatic mucinous carcinoma is strongly immunopositive for estrogen receptor. X200.

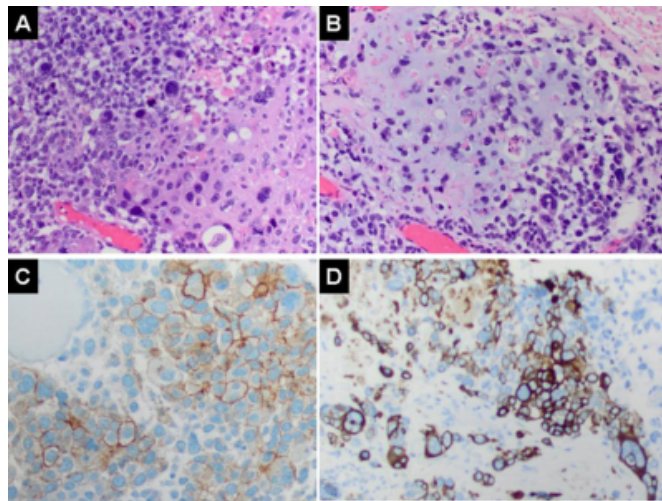


Case 2. A 41-year-old female was found to have a solitary nodule in her left breast on mammography. The biopsy and subsequent mastectomy showed a 1.9 cm metaplastic carcinoma with chondromyxoid metaplasia and squamous cell carcinoma component. Axillary lymph nodes were negative for metastatic carcinoma. Carcinoma cells were negative for ER, PR and HER-2/Neu. The patient underwent chemotherapy for treatment. Eleven months later, the patient developed headache and confusion. Brain MRI showed a ring-enhancing mass at the right occipital region measuring 3.1 x 2.7 x 2.0 cm with slight vasogenic edema and mild mass effect on the occipital horn of the right lateral ventricle (Fig. 1B). The tumor was grossly totally resected. The intra-operative cytology and frozen section diagnosis was metastatic carcinoma. The permanent sections showed a metaplastic carcinoma with predominant undifferentiated tumor cells with high nuclear/cytoplasmic ratio, scattered squamous cell carcinoma component, and chondroid component (Fig. 3). Immunohistochemical stains demonstrated carcinoma cells were positive for CK7 and E-cadherin, but negative for GCDFP-15, ER and Her-2/Neu (Fig. 3). There was focal patchy immunoreactivity of tumor cells for CD56 and synaptophysin, which indicated the neuroendocrine differentiation. Occasional tumor cell nuclei were positive for PR. The morphology and immunostain profiles of the brain metastasis were identical to the breast primary. CT demonstrated multifocal mediastinal and

bilateral hilar adenopathy, innumerable bilateral lung nodules and pleural based nodules consistent with metastases.

Figure 3

Metaplastic carcinoma with squamous differentiation. H&E stain. X400. Metaplastic carcinoma with chondroid differentiation. H&E stain. X400. The epithelial component of metaplastic carcinoma is immunopositive for E-cadherin. X400. The epithelial component of metaplastic carcinoma is immunopositive for CK-7. X400.



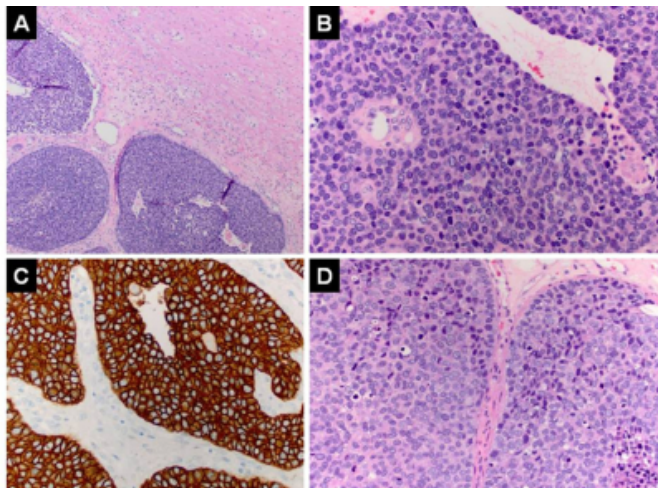
Case 3. A 71-year-old female presented with a 4-week complaint of blurry vision, decreased dexterity, and altered coordination of her left hand. She also complained of several episodes of confusion during which she was unable to recall where she lived. The patient denied any seizures, bowel/bladder incontinence, syncope, dizziness, or difficulty with ambulation. She was a non-smoker with a significant past medical history of diabetes mellitus type II, hypertension, hypercholesterolemia, and myocardial infarction approximately 12 years prior. The family history did not reveal any first degree relatives with cancer. Neurologic examination was remarkable only for mild left upper and lower extremity weakness. MRI of the brain revealed three supratentorial lesions suspicious for metastatic disease. There were a right 2.2 cm posterior parietal lesion, a left occipital 1.2 cm lesion and a 0.6 cm right parietal parasagittal lesion (Fig. 1C, 1D). Subsequent CT of her chest, abdomen, and pelvis revealed multiple pulmonary nodules, a distended appendix with inflammatory changes thought to either be a mucocele or neoplastic process measuring 0.8 cm, and a hypodense lesion on the thyroid gland.

The patient was brought to the operating room for a stereotactic guided right frontal craniotomy and excision of

tumor. Frozen section sent at the time of surgery showed metastatic carcinoma. The permanent sections and immunostains showed poorly differentiated non-small cell carcinoma, unclear origin. Carcinoma cells were positive for pan-cytokeratin AE1/AE3 and CK7, but negative for CK20, TTF-1, GCDFP-15, p63, synaptophysin, chromogranin, estrogen receptor, progesterone receptor and HER2/neu (Fig. 4). The patient tolerated surgery well and was discharged 3 days later with improving symptoms. Shortly afterwards, she underwent an endoscopy of upper GI tract, which was negative for any suspicious lesions. Within the next few weeks the patient had a breast ultrasound done followed by a biopsy. The pathology of the breast biopsy returned as moderately differentiated ductal cell carcinoma, which was negative for estrogen receptor, progesterone receptor and HER2/neu. The pathologist at our institution received both specimens and confirmed that breast carcinoma was morphologically identical to the metastatic carcinoma in the brain (Fig 4).

Figure 4

Metastatic carcinoma in the brain. Hematoxylin and eosin. X40. Metastatic carcinoma in the brain. H&E stain. X400. Metastatic carcinoma in the brain is strongly immunopositive for CK7. Invasive ductal carcinoma in the breast biopsy. H&E stain. X400.



DISCUSSION

Breast cancer is second after lung cancer as the most common cause of brain metastasis, occurring in 10-16% of patients suffering from breast cancer.¹⁵ Invasive ductal carcinoma (IDC) is the most common type of breast carcinoma, constituting approximately 70-85% of all invasive breast carcinoma.¹⁶ In over 80% of breast cancer cases, the woman discovers a lump on her breast herself, which is the most common symptom.¹⁷ The metastasis of

breast cancer to the brain is usually a late event. The median time from diagnosis of breast cancer to metastatic brain disease or leptomeningeal involvement is usually 2-3 years.^{16,17} In the majority of patients, spread to CNS occurs after other systemic metastases to lung, liver or bone are diagnosed.

Mucinous carcinoma and metaplastic carcinoma are two rare subtypes of breast carcinomas. Mucinous carcinoma has a favorable prognosis with low frequency of axillary lymph node metastasis and advanced metastatic disease.^{18,19} Our patient of case 1 had large mucinous carcinomas in bilateral breasts with positive axillary lymph nodes. After treatment, she had eight years free of disease before she finally developed brain metastasis without systemic metastatic disease and local recurrence. On the other hand, the metaplastic carcinoma is usually more aggressive than the conventional invasive ductal carcinoma.^{10,11} Our patient of case 2 had a small metaplastic carcinoma (1.9 cm) with negative axillary lymph nodes. Only after 11 months, she developed brain metastasis and systemic metastatic diseases.

Our patient of case 3 did not recognize any lumps on her breast nor had any signs of other systemic cancer involvement. Her initial complaint to her neurologist and primary care physician was that of blurred vision and confusion. After work up with brain MRI and surgery, a breast biopsy afterwards helped us confirm that the metastatic lesions in the brain were of breast origin. The patient had triple negative invasive ductal carcinoma, which did not express estrogen receptor (ER), progesterone receptor (PR) or human epidermal growth factor receptor-2 (HER2). Both triple negative invasive ductal carcinoma and metaplastic carcinoma have a worse prognosis.

These less aggressive subtypes of invasive breast carcinomas such as mucinous carcinoma need long-term follow-up. Brain CT or MRI for ruling out possible brain metastasis is warranted if the patient suddenly develops CNS symptom even after many years of remission. For these more aggressive subtypes of invasive breast carcinomas such as metaplastic carcinoma or triple negative invasive ductal carcinoma, early CNS imaging study is prudent. Although it is rare, breast carcinoma can present as a brain metastatic carcinoma with unknown primary before having the definitive diagnosis of breast cancer.

References

1. D'Ambrosio AL, Agazzi S. Prognosis in patients presenting with brain metastasis from an undiagnosed primary tumor. *Neurosurg.Focus.* 2007; 22: E7.

2. Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. *J Clin.Oncol.* 2004; 22: 3608-3617.
3. Crivellari D, Pagani O, Veronesi A et al. High incidence of central nervous system involvement in patients with metastatic or locally advanced breast cancer treated with epirubicin and docetaxel. *Ann Oncol.* 2001; 12: 353-356.
4. Ryberg M, Nielsen D, Osterlind K, Andersen PK, Skovsgaard T, Dombrowsky P. Predictors of central nervous system metastasis in patients with metastatic breast cancer. A competing risk analysis of 579 patients treated with epirubicin-based chemotherapy. *Breast Cancer Res.Treat.* 2005; 91: 217-225.
5. Abali H, Celik I. High incidence of central nervous system involvement in patients with breast cancer treated with epirubicin and docetaxel. *Am.J Clin.Oncol.* 2002; 25: 632-633.
6. Shao MM, Liu J, Vong JS et al. A subset of breast cancer predisposes to brain metastasis. *Med.Mol.Morphol.* 2011; 44: 15-20.
7. Di Saverio S, Gutierrez J, Avisar E. A retrospective review with long term follow up of 11,400 cases of pure mucinous breast carcinoma. *Breast Cancer Res.Treat.* 2008; 111: 541-547.
8. Barkley CR, Ligibel JA, Wong JS, Lipsitz S, Smith BL, Golshan M. Mucinous breast carcinoma: a large contemporary series. *Am.J Surg* 2008; 196: 549-551.
9. Paramo JC, Wilson C, Velarde D, Giraldo J, Poppiti RJ, Mesko TW. Pure mucinous carcinoma of the breast: is axillary staging necessary? *Ann Surg Oncol.* 2002; 9: 161-164.
10. Tavassoli FA, Devilee P. World Health Organization Classification of Tumours. Pathology & Genetics. Tumors of the Breast and Female Genital Organs IARC Press, Lyon, France, 2003.
11. Tot T. Metaplastic breast carcinoma: detection using histology and immunohistochemistry. In: Hayat MA, ed. *Methods of Cancer Diagnosis, Therapy and Prognosis.* Springer, Berlin, Germany, 2008; 275-290.
12. Chen YR, Lin TH, Chan SM et al. Bilateral choroidal metastases as the initial presentation of a small breast carcinoma: a case report. *Zhonghua Yi.Xue.Za Zhi.(Taipei)* 1998; 61: 99-103.
13. Martin PJ, Rivas LT, Martin PR, Ortin CA, Arcaya NJ, Cacho GJ. [Cavernous sinus syndrome: an initial expression of a breast carcinoma]. *Neurologia* 2005; 20: 153-155.
14. O'Gorman CS, Awad ZT, Given HF. Bilateral choroidal metastases as the initial presentation of breast carcinoma. *Ir.Med.J* 2001; 94: 85-86.
15. Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. *J Clin.Oncol.* 2004; 22: 3608-3617.
16. Toikkanen S, Pylkkanen L, Joensuu H. Invasive lobular carcinoma of the breast has better short- and long-term survival than invasive ductal carcinoma. *Br.J Cancer* 1997; 76: 1234-1240.
17. Vogel VG. Breast Disorders: Cancer. In: Justin L, Kaplan JL, Barbara P, eds. *Merck Manual of Diagnosis and Therapy.* 2008.
18. Barkley CR, Ligibel JA, Wong JS, Lipsitz S, Smith BL, Golshan M. Mucinous breast carcinoma: a large contemporary series. *Am.J Surg* 2008; 196: 549-551.
19. Paramo JC, Wilson C, Velarde D, Giraldo J, Poppiti RJ, Mesko TW. Pure mucinous carcinoma of the breast: is axillary staging necessary? *Ann Surg Oncol.* 2002; 9: 161-164.

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