

Isolated Cranial Mononeuropathy: An Unusual Initial Presentation and Disease Progression of Metastatic Carcinoma of the Breast

Case Report

A previously healthy 46-year-old woman presented in April 2010 with a 1-month history of right facial paresthesia with pain over the maxillary region. She began receiving carbamazepine for presumed trigeminal neuralgia and experienced some improvement of symptoms. Her neurologic symptoms persisted and she underwent a brain magnetic resonance imaging (MRI) scan that revealed a 2.2×1.3 cm mass within Meckel's cave that extended along V2 and V3 branches of the trigeminal nerve; this was concerning for perineural spread of tumor from a nasopharyngeal or salivary gland tumor.

A sinonasal endoscopy was performed and was essentially normal. Additional imaging with a dedicated cranial nerve brain MRI demonstrated the previously identified mass in Meckel's cave with extension of abnormal enhancement and thickening involving the cisternal portion of the trigeminal nerve and along V2 and V3 (Figs 1A and 1B, arrows). Multiple lytic lesions at the posterior vertex of the skull, the clivus, the right lateral aspect of C1, the dens, and the body of C2 were also identified. A positron emission tomography with concurrent computed tomography (PET/CT) revealed a 3.5×2.1 cm intensely ^{18}F -fluorodeoxyglucose (FDG)–avid left medial breast mass, and two moderately FDG-avid masses measuring 2.7×2.0 cm and 1.2×0.9 cm, in the upper outer quadrant of the right breast. There were also widespread lytic lesions in the thoracic osseous structures, in addition to the known lytic lesions in the skull base. Taking all this together, metastatic breast cancer was the presumed diagnosis.

The patient denied any nipple discharge, breast pain, mass, infection, or trauma. Her most recent mammogram a year before was reportedly normal. Her medical history was only significant for removal of a dermoid ovarian cyst 10 years before. She reached men-

arche at age 12 years and had been prescribed the oral contraceptive pill for 10 years. Her first child was born when the patient was age 38 years, and she reached menopause at age 44 years. She did not require hormone replacement therapy. Family history was significant for lung cancer and bladder cancer in two uncles, with no family history of breast or ovarian cancer. Her *BRCA* mutation status is unknown.

Physical examination was significant for reduced sensation to touch over the right maxillary facial region, with no other cranial nerve abnormalities. The rest of the neurologic examination was normal. Breast examination revealed a mobile, nontender, 3 cm mass in the right upper outer quadrant and an irregular 2×3 cm mass in the left upper inner quadrant. A diagnostic mammogram demonstrated a spiculated mass with architectural distortion and microcalcifications measuring $8.0 \times 5.8 \times 7.4$ cm in the left upper inner quadrant and a macrolobular mass within the right upper outer quadrant. Breast ultrasound revealed a $2.8 \times 2.1 \times 1.7$ cm spiculated, hypoechoic mass in the left breast and a $3.4 \times 2.1 \times 1.5$ cm macrolobular, hypoechoic mass in the right upper outer breast.

Ultrasound-guided core biopsy of the left breast mass revealed a grade 2 (Nottingham), estrogen receptor (ER)–positive (90%, strong intensity), progesterone receptor (PR)–negative, and human epidermal growth factor receptor 2 (*HER2*)/*neu*–negative (1+ via immunohistochemistry [IHC]) infiltrating ductal carcinoma (Fig 2A, hematoxylin and eosin staining, $\times 400$ magnification). Interestingly, ultrasound-guided core biopsy of the right breast mass revealed a morphologically distinct, ER-positive (95%, strong intensity), PR-positive (90%, strong intensity), and *HER2*/*neu*–negative (0 via IHC) infiltrating ductal carcinoma, signet ring cell variant with abundant intracytoplasmic mucin and eccentrically placed nuclei (Fig 2B, hematoxylin and eosin staining, $\times 400$ magnification). Fine-needle aspiration of the right ilium lesion revealed metastatic breast adenocarcinoma similar to that present in the left breast primary cancer, with a similar immunophenotypic receptor profile (positive for ER [93%], negative for PR, and *HER2*/*neu* was not overexpressed). Signet ring cells were not identified in the bone metastasis.

With involvement of the trigeminal nerve, lumbar puncture was performed. CSF analysis revealed a cell count of $1/\mu\text{L}$, protein concentration of 75 mg/dL, and glucose concentration of 74 mg/dL; cytology did not demonstrate any malignant cells present. These findings were not consistent with a diagnosis of leptomeningeal carcinomatosis. Neither CA-15.3/27.29 nor CA-125 was tested on the CSF. Given the patient's persistent neurologic symptoms, she received palliative radiation to the base of the skull via opposed lateral beams, with 3 Gy over 10 fractions for a total dose of 30 Gy over a 2-week period. Given the endocrine-sensitive and *HER2*/*neu*–negative nature of her tumor and her postmenopausal status on the basis of follicle stimulating hormone, luteinizing hormone, and estradiol laboratory parameters, she was prescribed an aromatase inhibitor, letrozole. For her bone metastases, monthly zoledronic acid infusions were initiated. She also continued to receive narcotic therapy for pain, gabapentin for neuralgia, and corticosteroids and antiemetic therapy for supportive care.

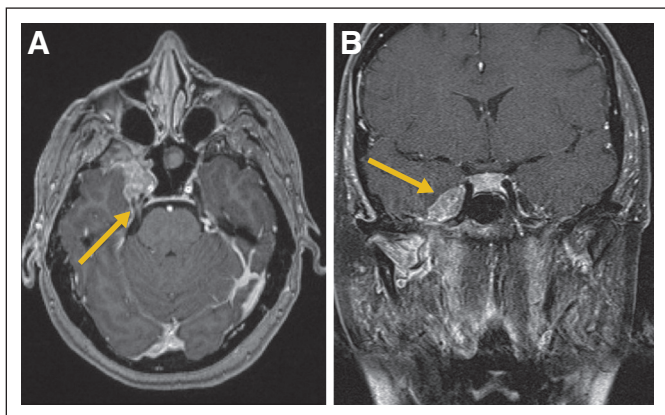


Fig 1.

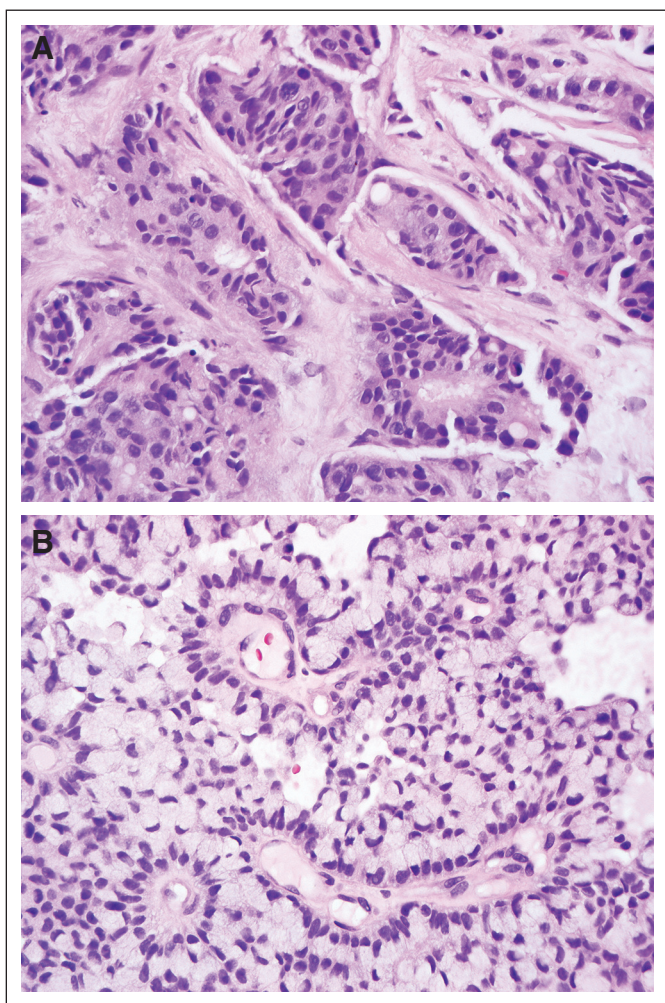


Fig 2.

By week 8 after initiation of radiation and systemic therapies, the patient's pain control had improved significantly, so that she was able to self-discontinue narcotics and continued to receive gabapentin. At 12 weeks, she underwent restaging studies. PET/CT imaging revealed a stable appearance of the left breast mass and decreased size of the right breast mass, with mixed responses of her widespread osseous metastatic disease. She continued to receive letrozole and monthly zoledronic acid infusion.

In January 2011, repeat PET/CT imaging revealed an increase in size of the left breast mass and left axillary lymph node. The patient was switched to second-line endocrine therapy with fulvestrant (Faslodex; AstraZeneca, Wilmington, DE). Repeat imaging in May 2011 continued to show disease progression, and she was switched to exemestane (Aromasin; Pfizer, New York, NY). In September 2011, she developed diplopia and was found to have a right sixth cranial nerve palsy. Given that repeat lumbar puncture was negative for leptomeningeal carcinomatosis, it was thought that the sixth cranial nerve palsy was a result of compression by bony metastasis in the right clivus within the skull. She was transitioned to tamoxifen. Repeat imaging in January 2012 demonstrated disease progression with increased liver metastases, and she was switched from endocrine therapy to chemotherapy with capecitabine. In July 2012, she presented with new left maxillary paresthesia.

Repeat brain MRI confirmed progression of disease with worsening involvement of the right trigeminal nerve and new involvement of the V2 and V3 branches of the left trigeminal nerve.

Because the patient was symptomatic neurologically, the decision was made to reirradiate with an additional 2 Gy over seven fractions for a total dose of 14 Gy (with opposed lateral beams), which she tolerated well. This low dose was given to limit the cumulative dose to the underlying optic apparatus. The patient has recently been transitioned to single-agent carboplatin chemotherapy, with reimaging scans scheduled at standard intervals.

Discussion

Although uncommon, cranial mononeuropathy has been reported in the literature as a manifestation of metastatic neoplasms. In the majority of cases, the neuropathy is caused by either diffuse metastasis to the leptomeninges¹ or dura mater,² or direct intracranial extension from invasive head and neck tumors. Solitary metastasis to an isolated cranial nerve from a distant primary tumor is rare but has been reported, particularly for trigeminal neuropathy in lung,³ lymphoma,⁴ colorectal cancer,⁵ and breast cancer.⁶⁻⁹

Similar to the reported cases, our patient presented initially with right trigeminal mononeuropathy, with improvement in symptoms after local and systemic therapy. She subsequently developed right abducens mononeuropathy and then left trigeminal mononeuropathy, indicating disease progression. Interestingly, throughout her clinical disease, she had no evidence of leptomeningeal carcinomatosis, which one would have expected, given the involvement of multiple cranial nerves. Although a paraneoplastic neuropathy could account for the multiple cranial nerve involvement,¹⁰ simultaneous neuropathies are usually reported and are not consistent with our patient's presentation, given initial brain MRI findings. Moreover, our patient had sequential involvement of multiple cranial nerves with disease progression, which, to our knowledge, has not been reported previously.

Another unique feature of our patient case is the presence of signet ring cells in the right breast biopsy. Signet ring cell carcinoma (SRCC) of the breast is uncommon, with an incidence of between 2% and 4.5% of total breast cancers.^{11,12} It is classified as a mucinous carcinoma and is defined by more than 20% of the malignant cells appearing as the signet ring form of tumor. On histology, metastatic gastric SRCC can be difficult to delineate from primary SRCC of the breast. It is important to differentiate the two because of their difference in prognosis. In our patient, the clinical presentation, the location of primary tumor(s) in the breast, and IHC stains that stained strongly for ER all confirmed a primary breast SRCC.

The prognosis of SRCC of the breast is unknown because of its rarity, but the presence of signet ring cells is believed to be a poor prognostic factor. A study by Frost et al¹³ found that the presence of 10% or more signet ring cells represents a poor individual prognostic factor in stage I infiltrating lobular carcinomas. The pure form of SRCC of the breast is also thought to be more aggressive than mucinous, ductal, or lobular invasive carcinoma; in 24 patients with SRCC, 60% survived less than 7 years.¹¹ Because we were unable to biopsy the cranial lesions, we can only speculate whether having features of SRCC of the breast could have accounted for this unusual presentation, with isolated metastasis to multiple cranial nerves.

In summary, we report the case of a patient with right facial paresthesia as the first clinical manifestation of metastatic breast cancer. Our patient case serves as a reminder to consider metastatic

disease as part of the differential diagnosis for patients presenting with trigeminal neuropathy.

*Ming Y. Lim, Sindu Chandramouleeswaran,
Timothy M. Zagar, Debra Budwit, and Carey K. Anders*
University of North Carolina, Chapel Hill, NC

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

REFERENCES

1. Rubinstein MK: Cranial mononeuropathy as the first sign of intracranial metastases. *Ann Intern Med* 70:49-54, 1969
2. Horton J, Means ED, Cunningham TJ, et al: The numb chin in breast cancer. *J Neurol Neurosurg Psychiatry* 36:211-216, 1973
3. Delaney P, Khoa N, Saini N: Isolated trigeminal neuropathy: An unusual complication of carcinoma of the lung. *JAMA* 237:2522-2523, 1977
4. Manon-Espaillet R, Lanska DJ, Ruff RL, et al: Visualization of isolated trigeminal nerve invasion by lymphoma using gadolinium-enhanced magnetic resonance imaging. *Neuroradiology* 32:531-532, 1990
5. Mastronardi L, Lunardi P, Osman Farah J, et al: Metastatic involvement of the Meckel's cave and trigeminal nerve: A case report. *J Neurooncol* 32:87-90, 1997
6. Nakano I, Iwasaki K, Kondo A: Solitary metastatic breast carcinoma in a trigeminal nerve mimicking a trigeminal neurinoma: Case report. *J Neurosurg* 85:677-680, 1996
7. Hirota N, Fujimoto T, Takahashi M, et al: Isolated trigeminal nerve metastases from breast cancer: An unusual cause of trigeminal mononeuropathy. *Surg Neurol* 49:558-561, 1998
8. Albayram S, Adaletli I, Selcuk H, et al: Breast cancer metastasis involving pterygopalatine fossa: A cause of trigeminal neuralgia. *Headache* 44:927-928, 2004
9. Moris G, Pérez-Peña M, Miranda E, et al: Trigeminal mononeuropathy: First clinical manifestation of breast cancer. *Eur Neurol* 54:212-213, 2005
10. Hammam T, McFadzean RM, Ironside JW: Anti-hu paraneoplastic syndrome presenting as bilateral sixth cranial nerve palsies. *J Neuroophthalmol* 25:101-104, 2005
11. Merino MJ, Livolsi VA: Signet ring carcinoma of the female breast: A clinicopathologic analysis of 24 cases. *Cancer* 48:1830-1837, 1981
12. Hull MT, Seo IS, Battersby JS, et al: Signet-ring cell carcinoma of the breast: A clinicopathologic study of 24 cases. *Am J Clin Pathol* 73:31-35, 1980
13. Frost AR, Terahata S, Yeh IT, et al: The significance of signet ring cells in infiltrating lobular carcinoma of the breast. *Arch Pathol Lab Med* 119:64-68, 1995

DOI: 10.1200/JCO.2012.47.3322; published online ahead of print at www.jco.org on May 13, 2013