Multifocal cranial nerve metastases mimicking benign neuropathy in HER2+ breast cancer: A case report

YEU-HAN CHIUEH[1], PEI-YU CHEN[2], DER-YANG CHO[1] and CHUN-CHUNG CHEN[1]

[1]Department of Neurosurgery, China Medical University Hospital, Taichung 404000, Taiwan, R.O.C.;
[2]Department of Pathology, China Medical University Hospital, Taichung 404000, Taiwan, R.O.C.

Received June 28, 2026; Accepted November 11, 2026

DOI: 10.3892/ol.2026.15971

Abstract. Breast cancer frequently metastasizes to the central nervous system (CNS), particularly in HER2+ subtypes; however, multifocal cranial nerve involvement is exceedingly rare and diagnostically challenging. The present study reports the case of a woman with HER2+ invasive ductal carcinoma who, ~14 months after resection of a solitary right cerebellar metastasis, developed progressive right facial numbness, dysphagia and facial palsy. Magnetic resonance imaging revealed new nodular enhancement involving the bilateral facial (VII), vestibulocochlear (VIII) and right trigeminal (V) nerves combined with a recurrent cerebellar lesion, clinically mimicking an inflammatory or infectious neuropathy. Given the oncological history of the patient, a tumor resection was performed and metastatic breast carcinoma immunophenotypically consistent with the primary tumor was confirmed. The patient subsequently received Gamma Knife radiosurgery and sequential systemic therapy (bevacizumab-etoposide-cisplatin, eribulin-trastuzumab and trastuzumab deruxtecan) for recurrent intracranial progression. At the last follow-up, ~5 months after the second surgery, facial palsy and dysphagia persisted despite transient postoperative improvement in facial pain and numbness, without evidence of extracranial disease. The present case, among the few reports describing multifocal (three-nerve) cranial nerve metastasis after prior curative-intent resection of an isolated brain metastasis, illustrates that such lesions can present as a delayed, aggressive and CNS-confined manifestation of HER2+ breast cancer despite sustained extracranial disease control. Early neuroimaging, tissue confirmation and multidisciplinary, sequential CNS-directed therapy are important for optimizing outcomes in this rare presentation.

Correspondence to: Professor Chun-Chung Chen, Department of Neurosurgery, China Medical University Hospital, 2 Yude Road, North District, Taichung 404000, Taiwan, R.O.C.
E-mail: 006407@tool.caaumed.org.tw

Key words: HER2+ breast cancer, cranial nerve metastasis, cranial neuropathy, leptomeningeal metastasis, magnetic resonance imaging, case report

Introduction

Breast cancer is one of the most frequent primary sources of central nervous system (CNS) metastases, second only to lung cancer in incidence (1). Epidemiological studies report brain metastases in 5-15% of patients with breast cancer (1), and autopsy series suggest a prevalence of up to 30% (1); in a large real-world cohort of patients with metastatic breast cancer, 24.6% developed brain metastases (2). Reported risk factors include HER2 positivity, hormone receptor negativity, triple-negative subtype, advanced stage at presentation, high histological grade, large tumor size, a high Ki-67 index and nodal involvement (1-3). The prognosis of patients with breast cancer brain metastases remains poor (3). In previous studies, among patients with HER2+ metastatic breast cancer, the median overall survival time was 26.3 months in those with CNS events compared with 44.6 months in those without (2), and the median overall survival time after the diagnosis of brain metastases was 13.2 months (3). With the advancement of systemic disease control through HER2-targeted therapies, including the monoclonal antibodies trastuzumab and pertuzumab, the antibody-drug conjugates ado-trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd), and the tyrosine kinase inhibitors lapatinib, neratinib and tucatinib (1,2), the pattern of disease recurrence has shifted toward an increased prevalence of CNS involvement. Overall, 30-50% of patients with HER2+ metastatic breast cancer develop brain metastases during their disease course, reflecting both improved extracranial survival and an intrinsic biological propensity for CNS dissemination (1-3).

While CNS metastases from breast cancer most commonly affect the brain parenchyma or leptomeninges, multifocal metastasis involving the cranial nerves is rare. Such presentations pose notable diagnostic challenges, as the clinical and radiographic manifestations can closely mimic inflammatory or infectious neuropathies. Cranial nerve metastasis typically occurs through direct perineural invasion, hematogenous dissemination to the skull base or leptomeningeal spread along cerebrospinal fluid pathways (4,5).

The present study reports the case of a woman with HER2+ invasive ductal carcinoma (IDC) who developed a solitary cerebellar metastasis which, ~14 months later, was followed by progressive cranial neuropathies associated with multifocal cranial nerve enhancement on brain magnetic resonance

imaging (MRI), and who subsequently experienced recurrent intracranial progression requiring sequential local and systemic therapy over the following months. To the best of our knowledge, the present case is among the few published reports of cranial nerve metastasis from breast cancer involving more than one nerve (6,7), and describes simultaneous three-nerve (V, VII and VIII) involvement emerging as a delayed relapse after curative-intent resection of a solitary brain metastasis in $HER2^+$ breast cancer. By detailing the complete diagnostic and therapeutic chronology, including the pathological distinction between the initial cerebellar and subsequent cerebellopontine (CP)-angle specimens, the aim of the present report is to raise awareness of this underrecognized pattern of CNS relapse and to underscore the importance of a low threshold for neuroimaging in patients presenting with new cranial neuropathies, even when extracranial disease remains well controlled.

Case report

Presentation. A 39-year-old woman presented with a palpable left breast mass at the 3 o'clock position (~2.8 cm in maximal diameter on ultrasonography) in October 2021. A core needle biopsy showed IDC, grade 2 according to the Nottingham histological grading system (8); the diagnosis was established by histomorphological examination of hematoxylin and eosin-stained sections, and immunohistochemistry was deferred to the surgical specimen. Staging investigations, including bone scans, chest computed tomography (CT) and breast ultrasonography, showed no evidence of distant metastasis and the clinical stage was cT2N0M0 (stage IIA) according to the American Joint Committee on Cancer (AJCC) staging system, 8th edition (9) (Fig. S1). The patient underwent left breast-conserving surgery with axillary lymph node dissection and oncoplasty in November 2021. Final histopathology upgraded the tumor to grade 3/3 IDC (Nottingham score 8/9 (8); 2.3-cm invasive focus) with associated high-grade ductal carcinoma *in situ* and lymphovascular invasion; the 12-o'clock margin was focally affected by ductal carcinoma *in situ*, while all invasive-carcinoma margins were clear. A total of 10/13 examined axillary lymph nodes contained metastatic carcinoma with extranodal extension. Immunohistochemistry demonstrated an estrogen receptor $(ER)^-$, progesterone receptor $(PgR)^-$ and $HER2^+$ (score 3+) profile with a Ki-67 proliferative index of 55%, yielding a final pathological stage of pT2N3a, cM0 (AJCC 8th edition pathological prognostic stage IIIB) (Fig. 1) (9-11). A summary of the complete diagnostic and therapeutic timeline is provided in Table I.

The patient received adjuvant chemotherapy between December 2021 and May 2022, consisting of docetaxel (116 mg, intravenously, every 3 weeks; four cycles) combined with dual HER2-targeted therapy [pertuzumab (840 mg loading dose followed by 420 mg, intravenously, every 3 weeks) and trastuzumab (600 mg, subcutaneously, every 3 weeks)], followed by epirubicin (140 mg) plus cyclophosphamide (780 mg) (intravenously, every 3 weeks; four cycles). A gonadotropin-releasing hormone agonist (triptorelin acetate; 3.75 mg, intramuscularly) was administered with each chemotherapy cycle for ovarian protection. Thereafter, the patient received maintenance oral tegafur-uracil (UFT; one capsule twice daily) from May 2022 to September 2023, and resumed pertuzumab and trastuzumab at the same doses until February 2023. Adjuvant intensity-modulated radiotherapy was delivered to the left breast, axilla and supraclavicular lymphatics (5,040 cGy in 28 fractions) with a simultaneous integrated boost to the tumor bed (5,880 cGy in 28 fractions) between June and July 2022, with only grade 1 acute skin toxicity and a complete treatment response.

In September 2023, ~14 months after completing adjuvant radiotherapy, the patient presented to the Emergency Department with a 1-month history of dizziness and a 3-day history of vomiting. The patient was afebrile and hemodynamically stable, with a Glasgow Coma Scale score of 15 (eye-opening, 4; verbal, 5; and motor, 6) (12), indicating that the patient was fully alert and oriented with no impairment of consciousness. The patient reported no headaches, head trauma, visual disturbances, dysphagia, dysarthria or focal weakness, and the laboratory tests, including a complete blood count, serum electrolytes, C-reactive protein, renal and liver function tests, were within normal limits. A brain MRI performed in September 2023, demonstrated an enhancing right cerebellar lesion (42x36x45 mm) with perifocal edema, mass effect on the fourth ventricle and brainstem, mild hydrocephalus and tonsillar herniation (Fig. 2A). The patient underwent a suboccipital craniectomy with tumor resection in September 2023 (surgery 1). Intraoperative frozen section analysis confirmed metastatic adenocarcinoma of mammary origin; final histopathology showed an immunoprofile of cytokeratin $(CK)7^+$, $CK20^-$, GATA binding protein 3 $(GATA3)^+$, ER^- (<1%), PgR^- and $HER2^+$ (score 3+), with a Ki-67 index of 70% (Table II; Fig. 3). Postoperatively, the dizziness resolved completely and the neurological examination was unremarkable. The patient subsequently received palliative brain irradiation (simultaneous integrated boost technique: 4,500 cGy in 15 fractions to the tumor bed and 3,000 cGy in 15 fractions to the whole brain, between October and November, 2023) and was started on T-DM1 (200 mg, intravenously, every 3 weeks; 14 cycles) in November 2023, with surveillance brain MRI performed regularly. Surveillance MRI ~1 year after surgery (September 2024) showed a stationary appearance of the operative site without abnormal enhancement, consistent with granulation tissue rather than recurrence (Fig. 2B), and T-DM1 was continued through August 2024, following which therapy was de-escalated to trastuzumab monotherapy (600 mg, subcutaneously, every 3 weeks; five doses between August and November 2024).

In November 2024, while receiving trastuzumab monotherapy, the patient developed new right facial numbness and progressive dysphagia. Neurological examination revealed preserved limb strength but a right peripheral facial palsy (House-Brackmann grade III) (13). Brain MRI performed in November 2024, revealed new nodular enhancement involving the bilateral facial (VII) and vestibulocochlear (VIII) nerve complexes and the right trigeminal (V) nerve, together with a new right cerebellar lesion (Fig. 4A and B) and a new enhancing focus in the left medial temporal lobe (Fig. 4C). In December 2024, the patient developed an acute headache, nausea, vomiting and right-sided visual disturbance; positron-emission tomography (PET)-CT showed no evidence of extracranial disease (Fig. 4D). Given the multifocal nodular enhancement pattern, the concurrent new parenchymal

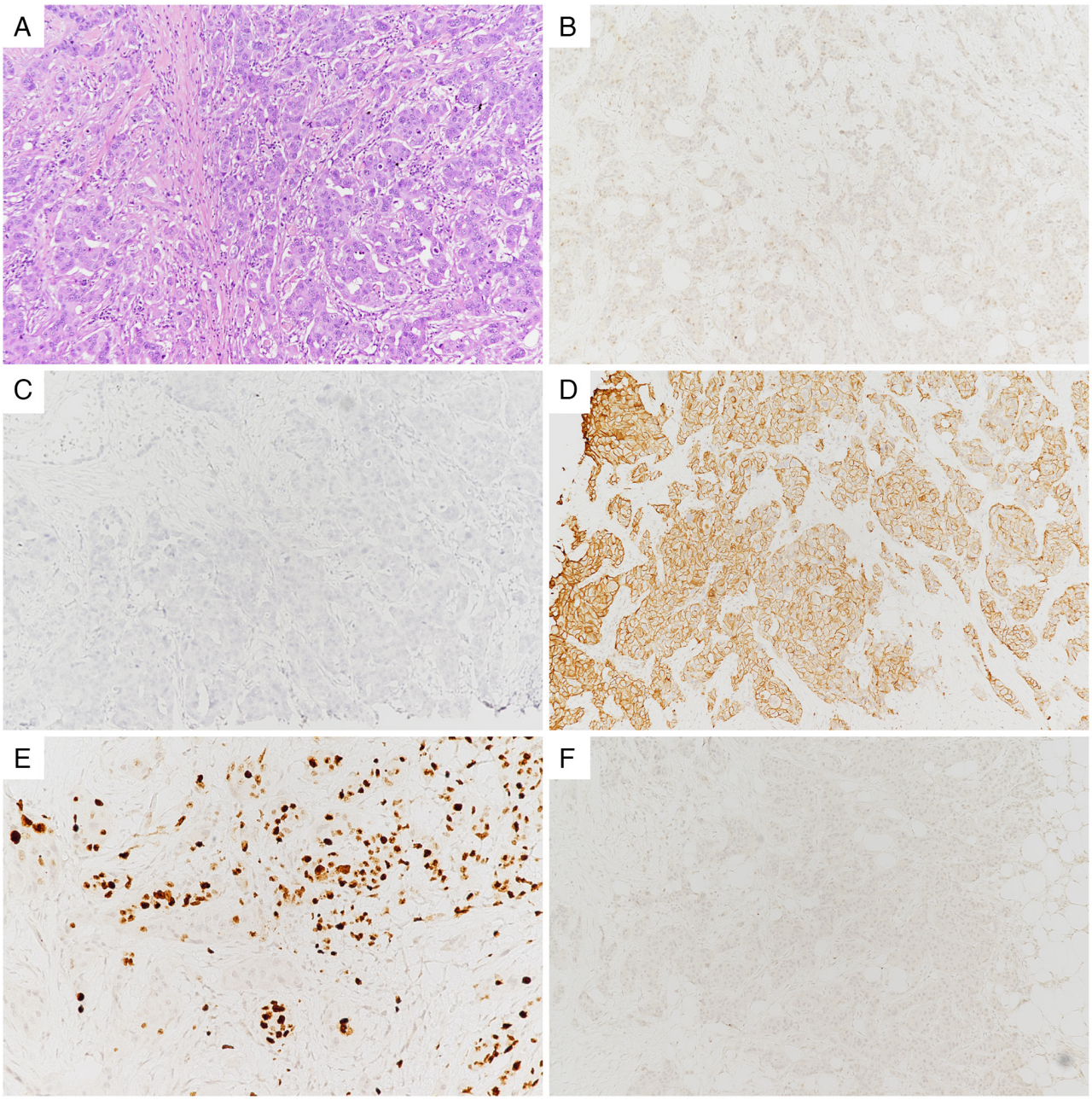


Figure 1. Representative photomicrographs of the primary left breast tumor (breast-conserving surgery, November 2021). (A) Hematoxylin and eosin stain showing grade 3 invasive ductal carcinoma composed of solid nests and trabeculae of tumor cells with marked nuclear pleomorphism, vesicular nuclei and prominent nucleoli infiltrating a desmoplastic stroma, with minimal tubule formation. Immunostaining showing a negative result for (B) estrogen receptor and (C) progesterone receptor expression in tumor cells, (D) strong, complete circumferential membranous staining for HER2 (score 3+), (E) Ki-67 nuclear staining (proliferative index, 55%) and (F) a lack of cytokeratin 5/14 staining in tumor cells. Original magnification, x100. Quantitative immunohistochemical scoring for each marker is summarized in Table II.

lesions and the oncological history, the present findings were considered highly concerning for metastatic rather than inflammatory or infectious disease. The bevacizumab, etoposide and cisplatin (BEEP) regimen [bevacizumab (300 mg, intravenously, on day 1), etoposide (100 mg/day, intravenously, on days 2-4) and cisplatin (100 mg, intravenously, on day 2)] was initiated in December 2024 for urgent intracranial disease control; trastuzumab (600 mg, subcutaneously) was continued at this cycle.

Just over 2 weeks after chemotherapy was initiated, the patient underwent a right retrosigmoid craniotomy with resection and decompression of the right CP-angle tumor in December 2024 (surgery 2). Histopathology confirmed metastatic carcinoma of breast origin, with tumor cells showing nuclear pleomorphism and foci of necrosis. Immunohistochemistry demonstrated GATA3 positivity, low ER positivity (8%), PgR negativity and HER2 positivity (score 3+), an immunoprofile consistent with, though not identical to, the original breast primary tumor and the 2023 cerebellar metastasis (Table II; Fig. 5), confirming that the multifocal cranial nerve lesions represented metastatic breast carcinoma rather than an inflammatory or infectious process. Postoperatively, the patient reported an improvement in facial pain and numbness, although the right facial palsy persisted

Table I. Chronological summary of the diagnostic and therapeutic course.

Date	Event
October 2021	Presentation with left breast mass (3 o'clock, ~2.8 cm in maximal diameter on ultrasonography); core needle biopsy: Grade 2 IDC (no immunohistochemistry performed); staging workup negative for metastasis; clinical stage cT2N0M0 (AJCC stage IIA)
November 2021	Left breast-conserving surgery with axillary lymph node dissection and oncoplasty. Final pathology: Grade 3/3 IDC (2.3 cm), high-grade ductal carcinoma *in situ*, lymphovascular space invasion-positive, 10/13 nodes positive with extranodal extension, $ER^-/PgR^-/HER2^+$ (3+)/Ki-67 55%; pT2N3a, cM0 (AJCC 8th edition pathological prognostic stage IIIB) (Fig. 1)
November 2021 (~3 weeks after breast-conserving surgery)	Port-A catheter placement
December 2021-May 2022	Adjuvant chemotherapy: Docetaxel x4 with pertuzumab + trastuzumab → epirubicin/cyclophosphamide x4; triptorelin with each cycle for ovarian protection
May 2022-September 2023	Maintenance tegafur-uracil; pertuzumab + trastuzumab resumed until February 2023
June-July 2022	Adjuvant IMRT: Left breast/axilla/supraclavicular fossa 5,040 cGy/28 fx plus simultaneous integrated boost to tumor bed 5,880 cGy/28 fx; grade 1 skin toxicity; complete response
September 2023	Brain MRI: Enhancing right cerebellar lesion (42x36x45 mm) with perifocal edema, 4th-ventricle/brainstem mass effect, mild hydrocephalus and tonsillar herniation (Fig. 2A)
September 2023 (1 day after brain MRI)	Surgery 1: Suboccipital craniectomy, right cerebellar tumor resection. Pathology: Metastatic adenocarcinoma (mammary origin); $CK7^+/CK20^-/GATA3^+/ER^-$ (<1%)/$PgR^-/HER2^+$ (3+)/Ki-67 70% (Fig. 3). Postoperatively: Dizziness resolved
October-November 2023	Palliative brain IMRT (SIB): Tumor bed 4,500 cGy/15 fx + whole brain 3,000 cGy/15 fx
November 2023-August 2024	T-DM1 every 3 weeks (14 cycles)
September 2024	Surveillance brain MRI (~1 year postoperatively): Stationary appearance of operative site without abnormal enhancement, consistent with granulation tissue (Fig. 2B)
August-November 2024	Regimen de-escalated to trastuzumab monotherapy (every 3 weeks; five doses)
November 2024	New right facial numbness, dysphagia. Exam: Right facial palsy (House-Brackmann III), limb strength preserved. Brain MRI: New nodular enhancement of bilateral facial (VII)/vestibulocochlear (VIII) nerves and right trigeminal (V) nerve, plus new right cerebellar lesion and new left medial temporal lobe focus (Fig. 4A-C)
December 2024 (19 days after brain MRI)	Acute headache, nausea/vomiting, right visual disturbance. PET-CT: No extracranial disease. BEEP regimen initiated (days 1-4), with continued trastuzumab
December 2024 (16 days after PET-CT)	Surgery 2: Right retrosigmoid craniotomy, resection/decompression of right cerebellopontine-angle tumor. Pathology: Metastatic carcinoma, breast origin; $GATA3^+$/ER 8% (low positive)/$PgR^-/HER2^+$ (3+) (Fig. 5). Postoperative findings: Facial pain and numbness improved; facial palsy persisted (House-Brackmann III)
December 2024 (5 days after surgery 2)	Gamma Knife radiosurgery: Multiple bilateral brain metastases (10 Gy to margin; mean dose, 11.1-12.9 Gy; 95-98% coverage)
February-March 2025	Systemic therapy changed to eribulin + trastuzumab (two cycles)
March 2025	Clinical progression (recurrent facial numbness, worsening dysphagia); re-treatment with BEEP regimen (March and April 2025)
April 2025	Progressive dysphagia (nasogastric tube twice declined); functional decline to wheelchair dependence. Brain MRI: More extensive enhancement in right internal auditory canal and right cerebellopontine-angle cistern/surface, with persistent left facial/vestibulocochlear, right trigeminal and left medial temporal lobe enhancement (Fig. 2C and D)
May 2025	Systemic therapy changed to T-DXd (one cycle) amid progressive neurological and radiographic findings
Last follow-up (May 2025)	Persistent right facial palsy and dysphagia, no new focal deficits, no evidence of extracranial disease; patient subsequently lost to follow-up

PET-CT, positron emission tomography-computed tomography; CK, cytokeratin; GATA3, GATA-binding protein 3; ER, estrogen receptor; PgR, progesterone receptor; Ki-67, marker of proliferation Ki-67; IDC, invasive ductal carcinoma; MRI, magnetic resonance imaging; IMRT (SIB), intensity-modulated radiotherapy with simultaneous integrated boost; fx, fractions; BEEP, bevacizumab, etoposide and cisplatin; AJCC, American Joint Committee on Cancer; T-DM1, ado-trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

Table II. Comparative immunohistochemical profile of sequential tumor specimens.

Specimen	Date	Estrogen receptor	Progesterone receptor	HER2	Marker of proliferation Ki-67	Other markers
Primary breast tumor	November 2021	Negative	Negative	Positive (3+)	55%	$CK5/14^-$
Cerebellar metastasis (surgery 1)	September 2023	Negative (<1%)	Negative	Positive (3+)	70%	$CK7^+$, $CK20^-$, $GATA3^+$
Cerebellopontine-angle metastasis (surgery 2)	December 2024	Low positive (8%)	Negative	Positive (3+)	Not performed	$GATA3^+$

CK, cytokeratin; GATA3, GATA-binding protein 3.

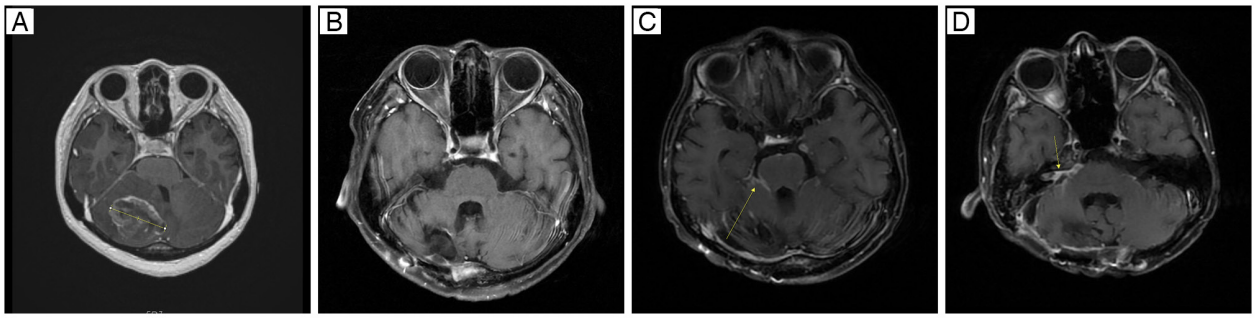


Figure 2. Serial axial T1-weighted contrast-enhanced brain MRI illustrating the initial cerebellar metastasis and its interval course. (A) Initial MRI (September 2023) showing an enhancing right cerebellar mass measuring 45 mm in maximal diameter (calipers), with mass effect on the fourth ventricle and brainstem. (B) Surveillance MRI ~1 year after cerebellar tumor resection (September 2024) showing a stationary appearance of the surgery site without abnormal enhancement, consistent with granulation tissue. (C and D) MRI obtained after the second (CP-angle) surgery (April 2025) demonstrating more extensive enhancement involving the (C) right CP-angle cistern and (D) right internal auditory canal, with extension along the CP-angle surface, in addition to persistent enhancing nodules involving the left facial/vestibulocochlear nerve complex, right trigeminal nerve and left medial temporal lobe (not all shown), findings consistent with further disease progression. MRI, magnetic resonance imaging; CP, cerebellopontine.

(House-Brackmann grade III). In December 2024, 5 days after surgery 2, the patient received Gamma Knife radiosurgery for multiple additional bilateral brain metastases (10 Gy to the tumor margin; mean dose, 11.1-12.9 Gy; 95-98% coverage).

Despite these interventions, the patient experienced repeated intracranial progression over the following months. Systemic therapy was changed to eribulin (2 mg, intravenously, on days 1 and 8 of a 21-day cycle) plus trastuzumab (600 mg, subcutaneously, on day 1) in February 2025. After two cycles, clinical progression, manifesting as recurrent facial numbness, progressively worsening dysphagia and poor appetite, was noted by mid-March 2025, prompting re-treatment with the BEEP regimen at the same doses in March and April 2025 (one cycle each). The patient twice declined nasogastric tube placement. Brain MRI performed in April 2025 demonstrated more extensive enhancement involving the right internal auditory canal and right CP-angle cistern, with extension along the CP-angle surface, together with persistent enhancing nodules involving the left facial/vestibulocochlear nerve complex, right trigeminal nerve and left medial temporal lobe, which was consistent with further disease progression at and around the second operative site (Fig. 2C and D). Systemic therapy was changed to T-DXd (200 mg, intravenously) in May 2025 in the context of these progressive neurological and radiographic findings; one cycle was administered before the patient was lost to follow-up. At the last follow-up, ~5 months after the second surgery, the patient exhibited persistent right facial palsy and dysphagia without new focal neurological deficits; they had become wheelchair-dependent due to overall functional decline but had no radiographic or clinical evidence of extracranial metastatic disease. The patient attended the outpatient clinic at each treatment visit, namely, every 3 weeks during T-DM1 and trastuzumab therapy and every 1-3 weeks during the subsequent chemotherapy, and contrast-enhanced brain MRI was performed in September 2024, November 2024 and April 2025.

Histopathology and immunohistochemistry. Tissue specimens were fixed in 10% neutral-buffered formalin for 6-72 h at room temperature and embedded in paraffin, and 4-μm sections were cut. Frozen sections of the intraoperative cerebellar specimen were cut at 4 μm in a cryostat at -20˚C. Hematoxylin and eosin staining used hematoxylin for 3 min and eosin for 1 min at room temperature (hematoxylin for 2 min on frozen sections). Immunohistochemistry was performed on a Leica BOND-III automated stainer (Leica Biosystems). Endogenous peroxidase was blocked with 3-4% (v/v) hydrogen peroxide for 5 min at room temperature (BOND Polymer Refine Detection kit, DS9800; Leica Biosystems). The following primary antibodies were incubated with the sections at room temperature: ER (clone SP1; 1:200; cat. no. Z2021RS; 30 min; Zeta Corporation), PgR (clone 16; 1:500; cat. no. NCL-L-PGR-312/2; 30 min;

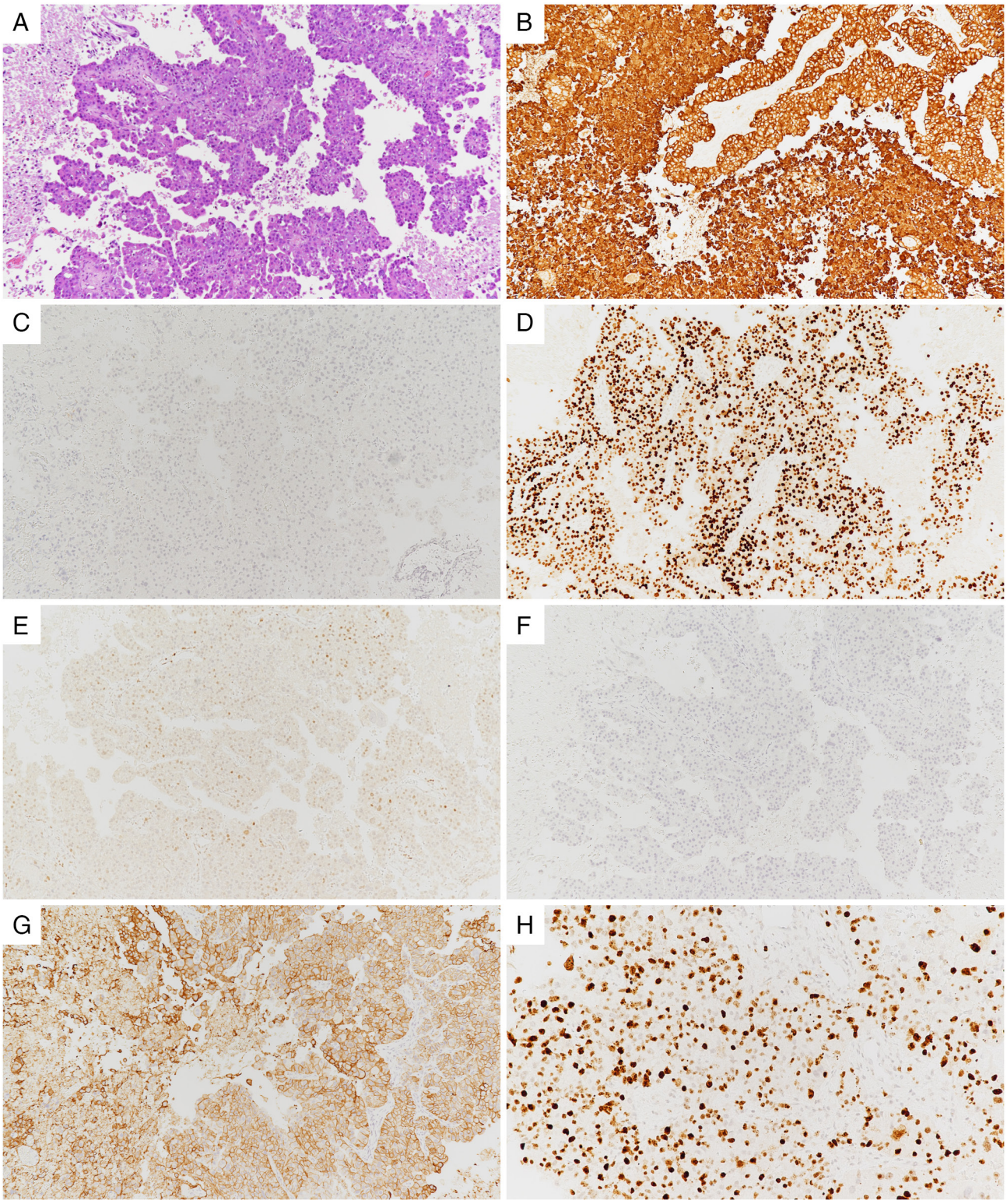


Figure 3. Representative photomicrographs of the right cerebellar metastasis (surgery 1, September 2023). (A) Hematoxylin and eosin stain showing cohesive nests and papillary-like clusters of pleomorphic tumor cells with adjacent necrotic debris, consistent with metastatic adenocarcinoma of mammary origin. Immunostaining showing (B) diffuse strong cytoplasmic positivity for CK7, (C) a lack of staining for CK20, (D) diffuse strong nuclear positivity for GATA-binding protein 3, a lack of (E) estrogen receptor (<1%) and (F) progesterone receptor expression, (G) strong, complete circumferential membranous staining for HER2 (score 3+) and (H) Ki-67 nuclear staining (proliferative index, 70%). Original magnification: x100 (A-G). Quantitative immunohistochemical scoring for each marker is summarized in Table II. Same fixation, processing, section thickness and H&E protocol as Fig 1; imaged on a Nikon ECLIPSE Ni light microscope (LED). CK, cytokeratin.

Leica Biosystems), HER2 (polyclonal; 1:3,500; cat. no. A0485; 20 min; Dako; Agilent Technologies, Inc.), Ki-67 (clone GM010; 1:1,000; cat. no. 61-0078; 20 min; Genemed Biotechnologies, Inc.), CK5/14 (clone XM26+LL002; 1:200; cat. no. ACI 3025C; 20 min; Biocare Medical, LLC), CK7 (clone RN7; 1:200; cat. no. NCL-L-CK7-560; 20 min; Leica

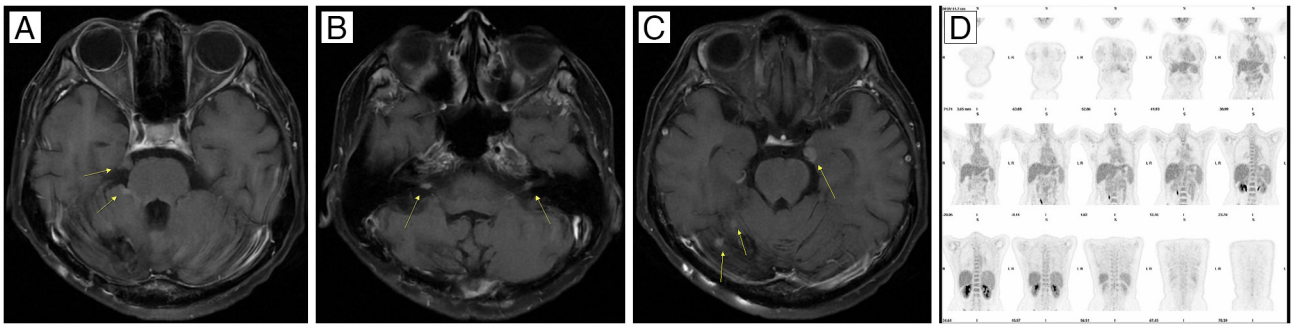


Figure 4. Brain MRI and PET findings at the time of cranial nerve involvement. (A-C) Images were obtained in November 2024: (A) Axial T1-weighted contrast-enhanced MRI. The superior yellow arrow indicates abnormal nodular enhancement along the right trigeminal nerve (cranial nerve V), and the inferior yellow arrow indicates an adjacent enhancing lesion in the right cerebellum, consistent with metastatic spread. (B) Axial T1-weighted contrast-enhanced brain MRI. The yellow arrows indicate abnormal nodular enhancement of the bilateral facial (VII) and vestibulocochlear (VIII) nerve complexes within the internal auditory canals. (C) Axial T1-weighted contrast-enhanced brain MRI showing enhanced metastatic foci in the right cerebellum (lower arrows) and the left medial temporal lobe (upper arrow). (D) Images were obtained in December 2024: Coronal PET images from PET-computed tomography showing no evidence of extracranial metastatic disease. MRI, magnetic resonance imaging; PET, positron emission tomography.

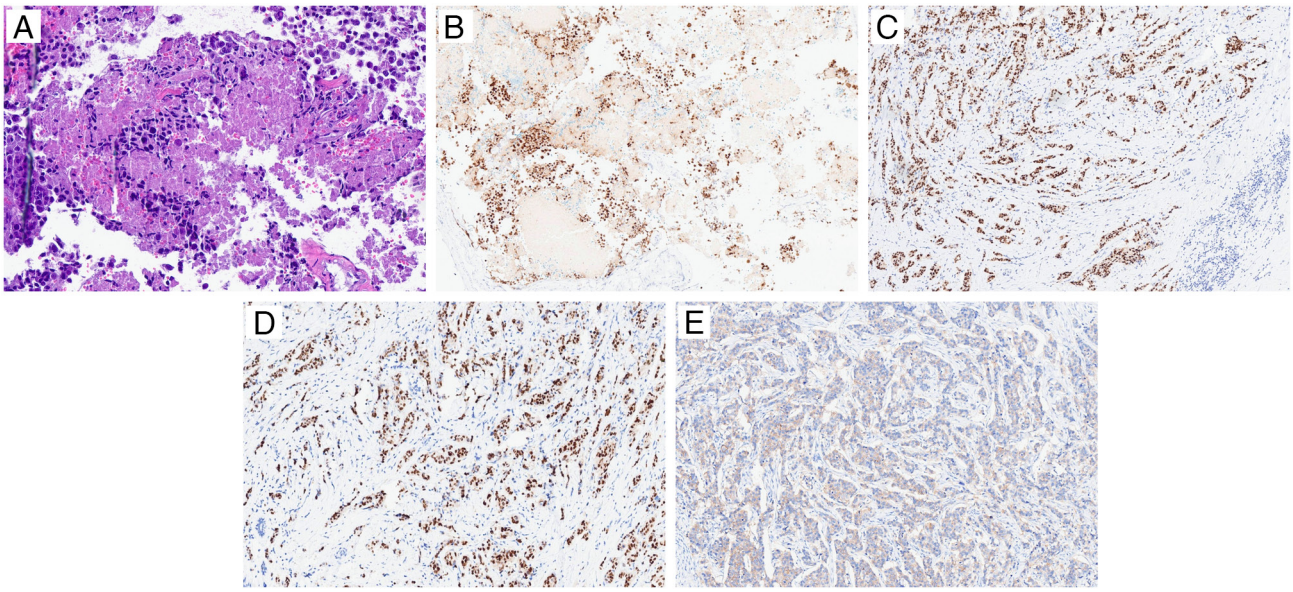


Figure 5. Representative photomicrographs of the right cerebellopontine-angle metastasis (surgery 2, December 2024). (A) Hematoxylin and eosin stain (original magnification, x40) showing nests and cords of tumor cells with nuclear pleomorphism and foci of necrosis. Immunostaining (original magnification, x20) showing (B) diffuse nuclear positivity for GATA-binding protein 3, (C) weak nuclear staining for estrogen receptor in 8% of tumor cells (low positive), (D) a lack of progesterone receptor expression and (E) strong, complete circumferential membranous staining for HER2 (score 3+). Quantitative immunohistochemical scoring for each marker is summarized in Table II.

Biosystems), CK20 (clone Ks20.8; 1:200; cat. no. 61-0018; 20 min; Genemed Biotechnologies, Inc.) and GATA3 (clone L50-823; 1:200; cat. no. Z2227; 30 min; Zeta Corporation). Detection used the BOND Polymer Refine Detection kit (cat. no. DS9800; Leica Biosystems) at room temperature for 20 min. Sections were examined on a Nikon ECLIPSE Ni light microscope with LED illumination (Nikon Corporation).

Discussion

Cranial nerve metastasis represents a distinct and particularly aggressive pattern of CNS dissemination in breast cancer. While parenchymal and leptomeningeal metastases have been well described, multifocal cranial nerve involvement remains a rare and underrecognized entity. In the present case, the subsequent development of nodular enhancement along multiple cranial nerves following the resection of a large cerebellar metastasis suggested diffuse leptomeningeal or perineural tumor spread, likely facilitated by the subarachnoid exposure of cranial nerve roots.

Epidemiological studies indicate that up to 55% of patients with metastatic HER2^{+} breast cancer eventually develop brain involvement, likely due to both intrinsic tumor biology that favors neural colonization and the limited penetration of systemic therapies across the blood-brain barrier (BBB), rendering the CNS a sanctuary site for tumor cells (2,3,14-16). The introduction of HER2-targeted agents, such as trastuzumab, pertuzumab and T-DM1, has markedly prolonged systemic disease control; however, this extended extracranial survival reveals the CNS to be a frequent site of relapse, as

circulating tumor cells have more time to colonize neural structures (17-19). This phenomenon is driven by a combination of pharmacokinetic limitation and intrinsic tumor biology. From a pharmacological standpoint, standard large-molecule targeted therapies (~150 kDa) cannot effectively cross the intact BBB, leaving the CNS to act as a sub-therapeutic sanctuary site. Biologically, $HER2^+$ breast cancer cells demonstrate a distinct neural tropism. Through the upregulation of specific signaling pathways and the potential secretion of matrix metalloproteinases, circulating tumor cells can breach the endothelial tight junctions of the BBB, colonize the leptomeningeal spaces and thrive within the neural microenvironment while systemic disease remains successfully suppressed (20,21). The disease course of the present patient, namely recurrent CNS-confined progression over >1 year despite consistently negative extracranial staging (PET-CT, December 2024), illustrates this sanctuary-site phenomenon clearly.

The diagnosis of cranial nerve metastasis relies primarily on contrast-enhanced MRI, which classically demonstrates linear or nodular enhancement along affected nerves, often in the CP angle or the peri-mesencephalic cisterns. The differential diagnosis for multifocal cranial nerve enhancement is broad and classically categorized into neoplastic, inflammatory/autoimmune and infectious etiologies. Distinguishing among these based solely on neuroimaging is a formidable clinical challenge. Among neoplastic etiologies beyond metastatic carcinoma, neurolymphomatosis can present with cranial neuropathy and characteristically demonstrate thickened or nodular enhancement. Inflammatory and granulomatous diseases, such as neurosarcoidosis and autoimmune neuropathies (such as Guillain-Barré syndrome), are major mimics (22). Guillain-Barré syndrome typically exhibits bilateral thickened enhancement. Neurosarcoidosis can present with nodular enhancement closely mimicking metastasis; however, it is usually accompanied by systemic manifestations, which were absent in the present case. Furthermore, infectious neuropathies, including viral neuritis, Lyme disease, neurosyphilis and tuberculous meningitis, can also cause multifocal cranial nerve enhancement. Viral neuritis and neurosyphilis typically induce linear enhancement (enhancement without an increase in nerve diameter), whereas Lyme disease and tuberculosis may cause thickened enhancement. These infections in tuberculosis are often complicated by prominent basal exudates, are accompanied by corresponding systemic symptoms or distinct cerebrospinal fluid (CSF) profiles (22). While non-malignant etiologies must be carefully considered, the clinical context remains paramount. For patients with a known history of $HER2^+$ breast cancer, the sudden onset of progressive, multifocal cranial neuropathies, especially when neuroimaging reveals a nodular enhancement pattern concurrent with new parenchymal brain lesions, should prioritize leptomeningeal or perineural metastatic dissemination (22,23).

The European Association of Neuro-Oncology-European Society for Medical Oncology guidelines state that, in patients with typical clinical signs and corresponding MRI abnormalities, leptomeningeal metastasis can be diagnosed as probable without cytological confirmation, whereas a confirmed diagnosis requires cytological or histological evidence. In the present case, CSF cytology was not obtained; instead definitive tissue diagnosis was achieved by surgical resection of the symptomatic CP-angle lesion (surgery 2), and the diagnosis therefore rested on combined clinical, radiographic and histopathological criteria, consistent with the standard of care (24,25).

Cranial nerve metastasis and diffuse leptomeningeal carcinomatosis are related but are biologically and prognostically distinct entities. Leptomeningeal metastasis, defined by diffuse tumor seeding of the subarachnoid space and typically confirmed by malignant cells on CSF cytology, carries a particularly poor prognosis, with a median survival time of only a few months even with treatment (25). Multifocal cranial nerve metastasis, as in the present patient, may instead reflect discrete nodular deposits along nerve sheaths without a diffuse leptomeningeal spread; CSF cytology was not obtained in the present case, and therefore a coexisting element of leptomeningeal disease cannot be entirely excluded. However, the disease of the patient behaved as a recurrently progressive, CNS-confined process, ultimately resulting in accumulating neurological disability, persistent facial palsy, worsening dysphagia and functional decline to wheelchair dependence over the ensuing months despite multimodal local and systemic therapy. This trajectory underscores that, even in the absence of confirmed diffuse leptomeningeal involvement, multifocal cranial nerve metastasis carries substantial morbidity and prognostic extrapolation from the leptomeningeal metastasis literature should be made cautiously.

The therapeutic management of cranial nerve metastasis requires a multimodal, sequential approach individualized to disease burden and prior therapy exposure. Surgical resection, performed twice in the present case, can relieve mass effect and nerve compression and provide tissue for diagnosis, while radiosurgery offers durable local control for residual or additional lesions. Selection of systemic therapy in this setting must account for both CNS penetration and prior treatment exposure: The patient had already received T-DM1 followed by trastuzumab maintenance before developing multifocal cranial nerve disease. Given the acuity of the presentation, the BEEP regimen was used initially for rapid cytoreduction (26), followed by eribulin plus continued trastuzumab, a combination with reported systemic and intracranial activity in $HER2^+$ disease, once the acute presentation had stabilized. With further intracranial progression despite these measures, therapy was escalated to T-DXd, an antibody-drug conjugate with demonstrated efficacy against both parenchymal and, increasingly, leptomeningeal $HER2^+$ disease (18,27,28). This stepwise escalation through cytotoxic, antibody-drug conjugate and CNS-directed local therapies illustrates the practical sequencing challenges that arise once the CNS becomes the dominant, and ultimately sole, site of relapse in an otherwise systemically controlled $HER2^+$ breast cancer.

Previously reported cases of cranial nerve metastasis from breast cancer have predominantly described the involvement of a single nerve, most commonly the trigeminal or facial nerve (4,5,22). Makuszewska *et al* (29) described a solitary metastasis to the labyrinthine segment of the facial nerve presenting as isolated facial palsy. Involvement of more than one nerve is rarer, and Lim *et al* (6) reported a 46-year-old woman with hormone receptor-positive, $HER2^-$ disease in whom right trigeminal neuropathy was the initial manifestation, followed over subsequent months by right abducens

and left trigeminal nerve involvement, with repeatedly negative CSF cytology. Madgula *et al* (7) reported the case of a 66-year-old woman in whom sequential fourth, third and sixth nerve palsies due to carcinomatous meningitis were the presenting feature of previously undiagnosed breast cancer. By contrast, the present patient had $HER2^+$ disease and developed simultaneous nodular involvement of three cranial nerves (V, VII and VIII), bilaterally for VII and VIII, ~14 months after curative-intent resection of an isolated cerebellar metastasis and without extracranial disease.

The present report has several limitations. First, cytological confirmation of leptomeningeal disease through CSF analysis was not obtained (histopathological confirmation was instead obtained by surgical resection), so a contribution of diffuse leptomeningeal spread cannot be entirely excluded. Secondly, the follow-up was limited to ~5 months after the second surgery; the disease remained active throughout this period, and the patient was subsequently lost to follow-up, so longer-term outcome data are not available. Thirdly, no molecular or next-generation sequencing analysis of the metastatic lesions was performed; such analysis might have identified actionable resistance mechanisms informing subsequent systemic therapy choices. Finally, as a single-patient case report, the findings and treatment sequence described cannot be generalized, and the specific rationale underlying each systemic therapy transition reflects individualized clinical decision-making rather than a systematic scheme applicable to all patients with similar presentations.

The present case illustrates that multifocal cranial nerve metastases can manifest as a delayed, recurrently progressive complication in $HER2^+$ breast cancer, occurring even after an initial period of durable disease control following resection of a solitary brain metastasis. The subsequent clinical course, marked by repeated intracranial progression, accumulating cranial neuropathies and preserved extracranial disease control, highlights the CNS as a persistent sanctuary site in this disease subtype. While the outcome of the present patient does not permit broad conclusions about optimal management, the clinical course suggests that multidisciplinary collaboration among medical oncologists, neurosurgeons and radiation oncologists, together with a low threshold for neuroimaging and tissue confirmation when new cranial neuropathies arise, is important for timely diagnosis. Further research, including molecular characterization of cranial nerve metastases and prospective evaluation of CNS-penetrant HER2-targeted agents such as T-DXd, is needed to inform management of this rare and likely underrecognized pattern of relapse.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YHC collected the clinical and laboratory examination data, and magnetic resonance imaging images of the present case, summarized the data and wrote the manuscript. CCC conceived the study, performed the surgical resections, was responsible for the neurosurgical management of the patient and interpreted the clinical data. DYC advised on patient treatment, including Gamma Knife radiosurgery planning, contributed to the analysis and interpretation of the patient data, and critically revised the manuscript. YHC and CCC confirm the authenticity of all the raw data. PYC provided the histopathological images and pathology reports and interpreted the pathological findings. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient involved in the present study was subjected to standard clinical practice and provided written informed consent for the publication of medical data and images.

Competing interests

The authors declare that they have no competing interests.

References

1. Giordano G, Griguolo G, Landriscina M, Meattini I, Carbone F, Leone A, Del Re M, Fogli S, Danesi R, Colamaria A and Dieci MV: Multidisciplinary management of HER2-positive breast cancer with brain metastases: An evidence-based pragmatic approach moving from pathophysiology to clinical data. Crit Rev Oncol Hematol 192: 104185, 2023.
2. Garcia-Alvarez A, Papakonstantinou A and Oliveira M: Brain metastases in HER2-positive breast cancer: Current and novel treatment strategies. Cancers (Basel) 13: 2927, 2021.
3. Laakmann E, Witzel I, Neunhöffer T, Park-Simon TW, Weide R, Riecke K, Polasik A, Schmidt M, Puppe J, Mundhenke C, *et al*: Characteristics of patients with brain metastases from human epidermal growth factor receptor 2-positive breast cancer: Subanalysis of brain metastases in breast cancer registry. ESMO Open 7: 100495, 2022.
4. Hoppe J, Kalckreuth T, Metelmann M, Rumpf JJ, Klagges S, Dietzsch S, Scherlach C, Kuhnt T, Kortmann RD and Seidel C: Skull base metastases with cranial nerve deficits: Clinical profile of a severe disease. Nervenarzt 93: 812-818, 2022.
5. Takahashi H: Neurological symptom management in breast cancer meningeal carcinomatosis. Transl Breast Cancer Res 6: 7, 2025.
6. Lim MY, Chandramouleeswaran S, Zagar TM, Budwit D and Anders CK: Isolated cranial mononeuropathy: An unusual initial presentation and disease progression of metastatic carcinoma of the breast. J Clin Oncol 31: e294-e296, 2013.
7. Madgula IM, Hemmerdinger CM and Clark P: Metastatic breast cancer presenting as sequential cranial nerve palsy: A case report. J Med Case Rep 8: 430, 2014.
8. Elston CW and Ellis IO: Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: Experience from a large study with long-term follow-up. Histopathology 19: 403-410, 1991.
9. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, *et al* (eds). AJCC Cancer Staging Manual. 8th edition. Springer, New York, NY, 2017.

10. Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, Allred DC, Bartlett JM, Bilous M, Fitzgibbons P, *et al*: Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American society of clinical oncology/college of American pathologists clinical practice guideline update. J Clin Oncol 31: 3997-4013, 2013.
11. Allison KH, Hammond MEH, Dowsett M, McKernin SE, Carey LA, Fitzgibbons PL, Hayes DF, Lakhani SR, Chavez-MacGregor M, Perlmutter J, *et al*: Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. J Clin Oncol 38: 1346-1366, 2020.
12. Teasdale G and Jennett B: Assessment of coma and impaired consciousness. A practical scale. Lancet 2: 81-84, 1974.
13. House JW and Brackmann DE: Facial nerve grading system. Otolaryngol Head Neck Surg 93: 146-147, 1985.
14. Kordbacheh T, Law WY and Smith IE: Sanctuary site leptomeningeal metastases in HER-2 positive breast cancer: A review in the era of trastuzumab. Breast 26: 54-58, 2016.
15. Witzel I, Oliveira-Ferrer L, Pantel K, Müller V and Wikman H: Breast cancer brain metastases: Biology and new clinical perspectives. Breast Cancer Res 18: 8, 2016.
16. Grinda T, Aizer AA, Lin NU and Sammons SL: Central nervous system metastases in breast cancer. Curr Treat Options Oncol 26: 14-35, 2025.
17. Bottosso M, Griguolo G, Sinoquet L, Guarascio MC, Aldegheri V, Miglietta F, Vernaci G, Barbieri C, Girardi F, Jacot W, *et al*: Prognostic impact of extracranial disease control in HER2+ breast cancer-related brain metastases. Br J Cancer 128: 1286-1293, 2023.
18. Zimmer AS, Van Swearingen AED and Anders CK: HER2-positive breast cancer brain metastasis: A new and exciting landscape. Cancer Rep (Hoboken) 5: e1274, 2022.
19. Li J, Zhen J, Ai R, Lai M, Wang H and Cai L: Intracranial management of HER-2 overexpression breast cancer with extensive volume or symptomatic brain metastases. Front Oncol 14: 1386909, 2024.
20. Momeny M, Saunus JM, Marturana F, Reed AE, Black D, Sala G, Iacobelli S, Holland JD, Yu D, Da Silva L, *et al*: Heregulin-HER3-HER2 signaling promotes matrix metalloproteinase-dependent blood-brain-barrier transendothelial migration of human breast cancer cell lines. Oncotarget 6: 3932-3946, 2015.
21. Warrior S, Cohen-Nowak A and Kumthekar P: Modern management and diagnostics in HER2+ breast cancer with CNS metastasis. Cancers (Basel) 15: 2908, 2023.
22. Moltoni G, Romano A, Blandino A, Palizzi S, Romano A, D'Arrigo B, Guarnera A, Dellepiane F, Frezza V, Gagliardo O, *et al*: Extra-axial cranial nerve enhancement: A pattern-based approach. Radiol Med 129: 118-132, 2024.
23. Wang N, Bertalan MS and Brastianos PK: Leptomeningeal metastasis from systemic cancer: Review and update on management. Cancer 124: 21-35, 2018.
24. Angus L, Martens JWM, van den Bent MJ, Smitt PAE, Sleijfer S and Jager A: Novel methods to diagnose leptomeningeal metastases in breast cancer. Neuro Oncol 21: 428-439, 2019.
25. Le Rhun E, Weller M, van den Bent M, Brandsma D, Furtner J, Rudà R, Schadendorf D, Seoane J, Tonn JC, Wesseling P, *et al*: Leptomeningeal metastasis from solid tumours: EANO-ESMO clinical practice guideline for diagnosis, treatment and follow-up. ESMO Open 8: 101624, 2023.
26. Lu YS, Chen TW, Lin CH, Yeh DC, Tseng LM, Wu PF, Rau KM, Chen BB, Chao TC, Huang SM, *et al*: Bevacizumab preconditioning followed by etoposide and cisplatin is highly effective in treating brain metastases of breast cancer progressing from whole-brain radiotherapy. Clin Cancer Res 21: 1851-1858, 2015.
27. Ratosa I, Dobnikar N, Bottosso M, Dieci MV, Jacot W, Pouderoux S, Ribnikar D, Sinoquet L, Guarneri V, Znidaric T, *et al*: Leptomeningeal metastases in patients with human epidermal growth factor receptor 2 positive breast cancer: Real-world data from a multicentric European cohort. Int J Cancer 151: 1355-1366, 2022.
28. Muller V, Bachelot T, Curigliano G, de Azambuja E, Furtner J, Gempt J, Jereczek-Fossa BA, Jerzak KJ, Rhun EL and Palmieri C: Expert consensus on the prevention of brain metastases in patients with HER2-positive breast cancer. Cancer Treat Rev 132: 102860, 2025.
29. Makuszewska M, Fus Ł, Bartoszewicz R and Niemczyk K: Solitary breast cancer metastasis to the facial nerve. Breast J 27: 838-840, 2021.

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