Case Report

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Painless Multiple Cranial Neuropathies due to Symptomatic Bone Marrow Metastasis in First Diagnosis of Advanced Stage Breast Cancer: A Case Report

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Abstract:

Metastatic breast cancer commonly involves the bone, liver, and lungs. While bone marrow metastasis (BMM) is rare, it has a significant association with distant recurrence and diminished survival rates. Typically, BMM manifests with hematological abnormalities and none of the previous reports revealed BMM as a first presentation in breast cancer patients. Herein is a reported case of painless, multiple cranial neuropathies as an unusual initial manifestation of symptomatic BMM, marking the first presentation of metastatic breast cancer.

Keywords: advanced-stage breast cancer, bone marrow metastasis, cranial neuropathies

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Introduction

Breast cancer is the most common cancer in females worldwide, with an age-standardized rate of 37.8 cases per 100,000 person-years. The mortality rate is 6.6% per year, which accounts for the third-ranking of all cancer deaths in Thailand[1].

The most common sites of metastases are in the bone, liver, and lung, with symptomatic bone marrow metastasis (BMM) being rarely reported in previous studies. Kopp et al. collected data of 12,970 breast cancer patients from 1995 to 2008 and found only 0.17% of patients with symptomatic bone marrow metastasis[2].

However, none of the previous reports detected BMM as the first presentation in breast cancer. Herein is the case report of an atypical presentation of symptomatic BMM in the first diagnosis of advanced-stage breast cancer.

Case report

A 47-year-old Thai female presented with numbness in her chin for 2 months. The numbness originated at both sides of the chin and gradually extended to the right cheek, while having a sparing angle of mandible. No chewing problems were observed.

One month prior to the outpatient visit, she developed painless horizontal binocular diplopia, which was worsening when looking to the left and at farsighted objects: no drooping of the eyelids was reported. In addition, she also suffered a generalized throbbing headache without increased intracranial pressure symptoms. There was no facial palsy, dysphagia, dysarthria, or visual acuity disturbance. Neither motor weakness nor numbness in other areas were described. She did not have a fever, weight loss, or other constitutional symptoms. She denied any underlying diseases. Eleven months prior to visiting the hospital, she had a history of bilateral total mastectomy without histopathology examination, due to cosmetic purposes.

Her physical examination revealed a mildly pale conjunctiva. The chest wall showed post-bilateral mastectomy scarring without palpable mass. No organomegaly nor lymphadenopathy was detected. The neurological examination revealed an abduction deficit of the left eye without ptosis, and preserved normal pupillary light reflexes of both eyes. There was decreased pinprick sensation of the right 2nd and 3rd branch of the Trigeminal nerve as well as the left 3rd branch of the Trigeminal nerve. The muscle of mastication was not atrophic and preserved normal power. The corneal reflex was within normal limits. Other physical examinations were unremarkable.

Her complete blood count showed bicytopenia with hemoglobin at 9.0 g/dL, platelet 85,000 cells/μL and a normal white blood cell count, whilst her lactate dehydrogenase level was elevated at 715 U/L (normal control 125-220 U/L). Magnetic resonance imaging (MRI) of the brain and skull base showed abnormal bone marrow signals of clivus, bilateral greater sphenoid wings and both petrous apex, which were suggestive of metastases or other bone marrow pathology (Figure 1). In order to search for the primary cancer, computerized tomography (CT) of the chest and whole abdomen were performed, which showed negative findings for malignancy. Following the clinical clues of bicytopenia and the bone marrow lesion in the skull base, bone marrow aspiration and biopsy were performed at the posterior superior iliac spine. These revealed extensive involvement of metastatic poorly differentiated carcinoma with focal tumor necrosis. The immunohistochemistry study showed that the tumor cells were positive for AE1/AE3, CK7, GCDFP15 (focally), E-cadherin, ER (90%), PR (15%) and HER2 (3+), but negative for CK20, TTF1, CDX2, P63, CD3, CD20, CD34, CD117 and MPO. Mucicarmine staining was also performed and showed negative results: EBER in situ hybridization was also negative. Her histomorphology and immunohistochemical profile were consistent with metastatic

breast cancer (Figure 2). The differential diagnosis for this subtype of breast cancer were invasive ductal carcinoma of no special type and metaplastic carcinoma. The latter could not be excluded due to a lack of the primary breast lesion. Therefore, the final diagnosis was advanced-stage, triple-positive breast cancer with bone marrow metastases. The patient then received chemotherapy combined with targeted therapy as dual anti-HER2 therapy. After the fourth cycle of weekly paclitaxel and the second cycle of trastuzumab and pertuzumab, the facial numbness improved, and binocular diplopia was completely resolved. However, follow-up MRI imaging showed no significant change in the extension of the abnormal marrow signal at the base of her skull (Figure 1). Presently, the treatment plan is to continue chemotherapy along with dual anti-HER2 therapy, then re-evaluate the response after complete treatment.

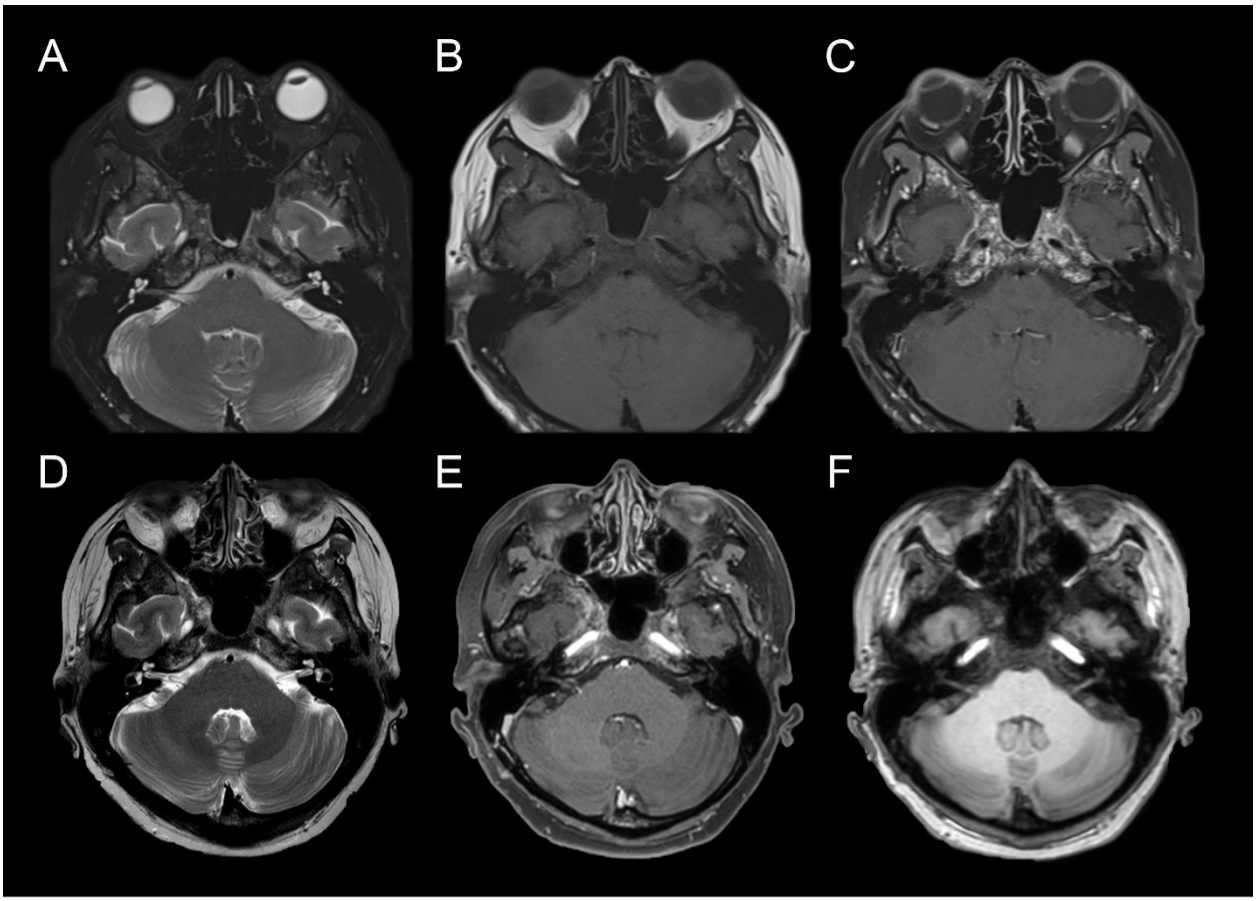

Figure 1 MRI of the brain axial view; comparing pre-treatment and post-treatment with systemic chemotherapy and dual-antiHER2. T2-weighted fat-suppressed image (A), T1-weighted image (B) and post-gadolinium T1-weighted fat-suppressed image (C) of pre-treatment showed an abnormal marrow signal, with enhancement of the clivus, petrous apex and bilateral greater sphenoid wings. After sessions of systemic treatment, no significant change in extension of the abnormal marrow signal at the base of the skull was seen, as shown in the T2-weighted fat-suppressed image (D), T1-weighted image (E) and post-gadolinium T1-weighted fat-suppressed image (F).

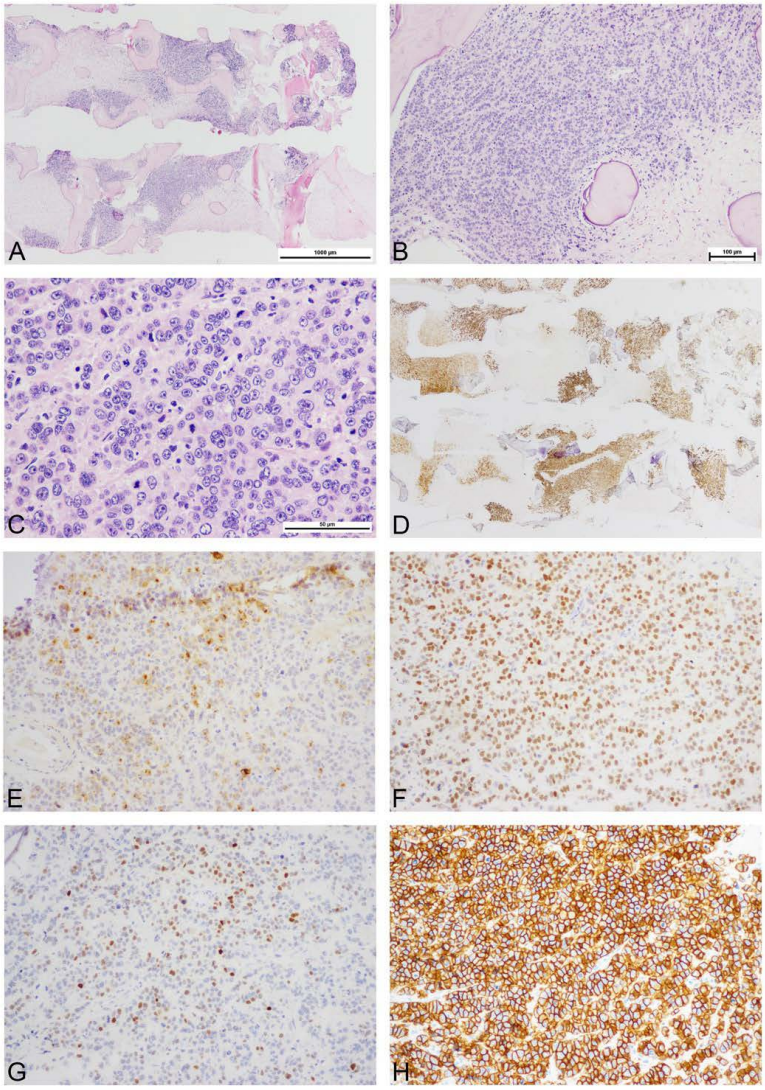

Figure 2 The bone marrow biopsy with hematoxylin and eosin (H&E) staining as well as immunohistochemical staining of the tumor. (A–B) Microscopically, the tumor extensively infiltrates into the marrow area, without any remaining hematopoietic cells (H&E stain, 20x, 100x). (C) The tumor cells arrange in a solid sheet and show marked nuclear pleomorphism, enlarged nuclei, vesicular chromatin, prominent nucleoli, and moderate eosinophilic cytoplasm. Brisk mitoses are noted (H&E stain, 400x). (D) AE1/AE3 highlights the tumor cell areas (20x). (E) GCDPF15 focally stains in the cytoplasm of tumor cells (200x). (F) ER shows strong nuclear staining in most tumor cells (200x). (G) PR shows focal nuclear staining (200x). (H) HER2 shows diffusely strong and complete membranous staining, which is considered positive 3+ (200x).

Discussion

Although BMM is common in hematologic malignancy, it is considered a rare condition in solid tumors, occurring in less than 10% of patients[3,4]. This case report demonstrates a BMM of triple-positive breast cancer.

Bone marrow metastatic breast cancer was first reported in 1980 by Coombes et al[5]. The incidence of pathologically proven BMM in primary or metastatic breast cancer ranges between 3% and 25%[6–8]. The common sites of BMM of breast cancer are the spine and ribs, while skull marrow metastasis is rare[8,9]. The median time from initial breast cancer diagnosis to bone marrow involvement in the previous studies ranged between 36 and 46 months. Moreover, patients having HER2 expression developed BMM earlier than HER2 negative patients[2,10].

Breast cancer patients having been diagnosed with BMM usually present with hematologic abnormalities. The most common hematological findings have been anemia with thrombocytopenia, thrombocytopenia and anemia, respectively[9,10]. Neurological presentations have also been reported. Focal headaches and cranial neuropathies have been the two main clinical features of skull metastasis, and certain clinical features might suggest the site of BMM.

Based on the anatomy, skull metastasis is classically categorized into calvarium and skull base metastasis. Calvarium metastases directly invade the dura and intradural space, leading to increased intracranial pressure, meningeal irritation and focal neurological signs. In a similar manner, skull base metastases straightforwardly infiltrate the foramen and cranial nerve, resulting in multiple cranial neuropathies[11]. However, the neurological deficit due to compressive lesions cannot definitely differentiate the origin of metastatic tumors between bone marrow, bony cortex and dura. The chronological presentation of pain may suggest the origin of a metastatic tumor. The metastasis to the bony cortex and dura usually develops as early focal pain due to it directly stimulating pain-sensitive structures on the periosteum. In contrast, the focal pain in BMM rarely develops: unless the tumor cells invade and destroy the bone tissue matrix from the marrow cavity[6]. Our patient presented with multiple, painless cranial neuropathies; raising suspicion of the BMM. All of the cranial nerves that were affected had cranial foramina in adjacent areas of the skull base. The possible mechanism of cranial neuropathies is that BMM has been gradually and continuously causing bone remodeling and thickening without breaking the bony cortex stretching the periosteum. Thus, the cranial nerves were injured by pressure effect. This hypothesis was supported by the MRI study that showed pressure effect with the preservation of the bony cortex.

Several investigations have been conducted to evaluate and detect skull metastasis and BMM. MRI has proven to be highly sensitive, and a useful method for demonstrating any invasion into the dura or cranial nerves. There is also a strong correlation between abnormal MRI findings in the marrow and the early development of clinical metastatic disease in patients with stage II-III breast cancer[12]. In contrast, CT scanning with bone windows is effective in revealing lytic bone lesions. However, CT scanning does not provide a clear visualization of boundaries, nor the degree of dural invasion caused by bone metastasis[11].

The presence of BMM in patients with breast cancer has shown a strong correlation between BMM and distant relapse in addition to poorer survival[13]. It has been suggested that once cancer reaches the bone marrow, most micrometastases are killed by the hostile microenvironment. However, some micrometastases enter a state of dormancy and recur steadily over many years, leading to incurable diseases[14]. Although it is incurable, systemic therapy shows a clinical benefit in regards to prolonged survival[10]. There is a proven systemic treatment for breast cancer expressing

HER2 receptors. Both trastuzumab and pertuzumab are humanized monoclonal antibodies against HER2 and have shown significant benefits in treatment, leading to a significant improvement in overall survival. Preclinical studies conducted using in vitro and xenograft models have demonstrated synergistic effects when pertuzumab and trastuzumab are combined. In a clinical evaluation of pertuzumab and trastuzumab study[15], a large phase III randomized trial involving 808 breast cancer patients, the added benefit of pertuzumab when combined with trastuzumab and docetaxel was demonstrated. The study showed an increased median overall survival from 40.8 months with docetaxel and trastuzumab alone to 56.5 months with the addition of pertuzumab to docetaxel and trastuzumab. This represented a 32% reduction in mortality. Additionally, at the 8-year long-term follow-up, 37% of patients with metastatic disease treated with the combination were still alive. This combination therapy has now become the standard of care for the first-line treatment of HER2-positive metastatic breast cancer.

Conclusion

Symptomatic BMM is considered a rare occurrence in solid tumors and even rarer than the initial presentation with skull marrow metastasis. The main clinical features of skull marrow metastasis are focal headache and cranial neuropathies, which vary depending on the site of BMM. These symptoms often prompt further investigations by clinicians, leading to suspicions about the origin of the primary tumor. Focusing on breast cancer patients, BMM has been found to be strongly correlated with distant relapse and poorer survival. However, systemic chemotherapy has been shown to improve overall survival in these patients.

Author contribution

SL: Conceptualization, writing-original draft. JT: writing-review & editing. NS: writing-review & editing PK: supervision all authors reviewed and approved the manuscript before submission.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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