Journal on Surgery

www.journalonsurgery.org

Case Report

Open Access, Volume 3

Brain Metastasis in HER2-Positive Breast Cancer: Case Report and Review of Literature

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Abstract

Introduction: Breast cancer (BC) is one of the most common cancers in women in developed countries. Approximately 15 to 20% of patients with BC have tumors with elevated levels of Human Epidermal Growth Factor Receptor 2 (HER2), which are associated with an aggressive clinical phenotype and poor prognosis. Brain metastases (BM) appears in more than 15% in the HER2-positive breast cancer population, which cause serious decrease in survival.

Presentation of case: We report a case of a 40-year-old female with HER2-positive invasive ductal carcinoma of the left breast that underwent neoadjuvant chemotherapy with dual HER2 blockage and nipple-sparing mastectomy with sentinel lymph node biopsy and adjuvant treatment. After four months, she experienced headaches and dizziness. Brain Magnetic Resonance Imaging (MRI) revealed a 17 x 19 mm polycyclic contour lesion in the left occipital lobe surrounded by perifocal edema. She underwent craniotomy and final pathological examination revealed BM of the breast cancer. Patient was treated with further HER2 blockage and stereotactic radiotherapy. Here, we report a successful combined local and systemic treatment approach for a HER2-poitive breast cancer with single site brain metastasis at 41 months follow-up.

Conclusion: The combination of local and systemic therapies was effective in reducing the recurrence of HER2-positive BCBM. To date, our patient has no signs of relapsed tumor. With a new anti-HER2 therapy agents, the overall survival of patients with BM are like to improve over time.

Manuscript Information: *Received: Mar 31, 2023; Accepted: May 09, 2023; Published: May 16, 2023*

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Citation: *Ostapenko E, Kogut A, Ostapenko A, Petroška D, Ostapenko V. Brain Metastasis in HER2-Positive Breast Cancer: Case Report and Review of Literature. J Surgery. 2023; 3(1): 1097.*

Introduction

In 2020, there were 2.3 million women were diagnosed with breast cancer and 685000 deaths globally. As of the end of 2020, there were 7.8 million women diagnosed with breast cancer in the past 5 years, making it the world's most prevalent cancer [1]. Patients with human epidermal growth factor receptor 2 (HER2) subtype represent approximately 15%-20% of breast cancers, which are related with an aggressive behavior, high distant recurrence rates, especially brain metastases [2]. Up to 31% of patients with HER2-positive metastatic BC will develop BM during the course of the disease, which often leads to worse morbidity and shorter survival. The main risk factors associated with increased brain metastases have been identified, including hormone receptor negative status, larger tumor size or higher tumor grade, younger age, and metastases to four or more axillary lymph nodes at the time of diagnosis [3]. The most common symptoms of BC brain metastases are headache, nausea, visual disturbances and vomiting [3]. BM are managed with local therapies, including surgical resection, stereotactic radiosurgery, stereotactic radiotherapy, and Whole-Brain Radiotherapy (WBRT). However, mean survival after local therapy remains very low ranging from 2 to 16 months, depending on involvement of the CNS and breast cancer subtype [4]. In the last decades, the development of anti-HER2 therapy have improved quality of life and overall survival in patients with metastatic breast cancer. These new alternatives, such as small-molecule tyrosine-kinase inhibitors (TKIs) and antibody-drug conjugates also increase the different treatment sequence possibilities for each clinical case. In this clinical case we report a successful combined local and systemic approach for HER2-positive BCBM at 41 months of follow-up.

Case presentation

A 40-year-old female patient from Lithuania presented to the National Cancer Institute (NCI) with the mass in her right breast. The patient had no family history of breast cancer. On physical examination, patient had a large mass measuring 8 x 7 cm involving the entire lower quadrant. There were also palpable axillary lymph nodes up to 3 cm. The patient's left breast was normal on palpation. Her diagnostic assessment included mammography and computed tomography, which showed a high-density, smoothly contoured mass with well-circumscribed margins in the right breast measuring 10 x 7 cm, 1,2 x 2 cm. An enlarged conglomerate of several metastatic lymph nodes up to 4.4 cm in the right axilla was observed. A core needle biopsy of the right breast mass revealed invasive ductal carcinoma with negative estrogen and progesterone receptors, HER2 positive receptors, and Ki-67 30% (Figure 1). There was no lymphovascular invasion or ductal carcinoma in situ component. The clinical diagnosis was cT2N3M0 stage IIIc and, HER2+. Chest, abdomen and pelvis tomography at that time showed no evidence of metastatic disease. Additionally, the patient underwent genetic testing that revealed no detrimental germline mutations in BRCA1 and BRCA2. The patient was scheduled for neoadjuvant therapy with pertuzumab in combination with trastuzumab and docetaxel. The first chemotherapy cycle was initiated with intravenous (IV) injection of pertuzumab 840 mg, trastuzumab 8 mg/m^2, and docetaxel 75 mg/m^2 on day 1 of the cycle. Similarly, her 2nd, 3rd, 4th, 5th, and 6th chemotherapy cycles were administered. The assessment was performed every 2 cycles. Magnetic resonance imaging (MRI) was performed after the 6th cycle, demonstrated a partial regression. Brain, thoracic, and abdominal CT tomography showed no signs of metastasis. Additionally, Positron Emission Tomograph-Computed Tomography (PET-CT) scanning was performed and showed no evidence of metastatic disease. The surgical intervention was indicated, and a right nipple-sparing mastectomy (NSM) with sentinel lymph node biopsy was performed. Final pathological examination – invasive ductal carcinoma measuring 6 mm in diameter with positive estrogen (40%), progesterone (20%), and HER2 receptors (Figure 1). No metastases were observed in the axillary nodes. The pathological disease stage was ypT1miN0(sn)M0, which corresponded to stage IA. All surgical margins were negative. After nipple- sparing mastectomy adjuvant radiotherapy (breast area 50 Gy and axilla 50 Gy) and adjuvant chemotherapy were carried out. Trastuzumab and Pertuzumab were administered every 28 days. The patient

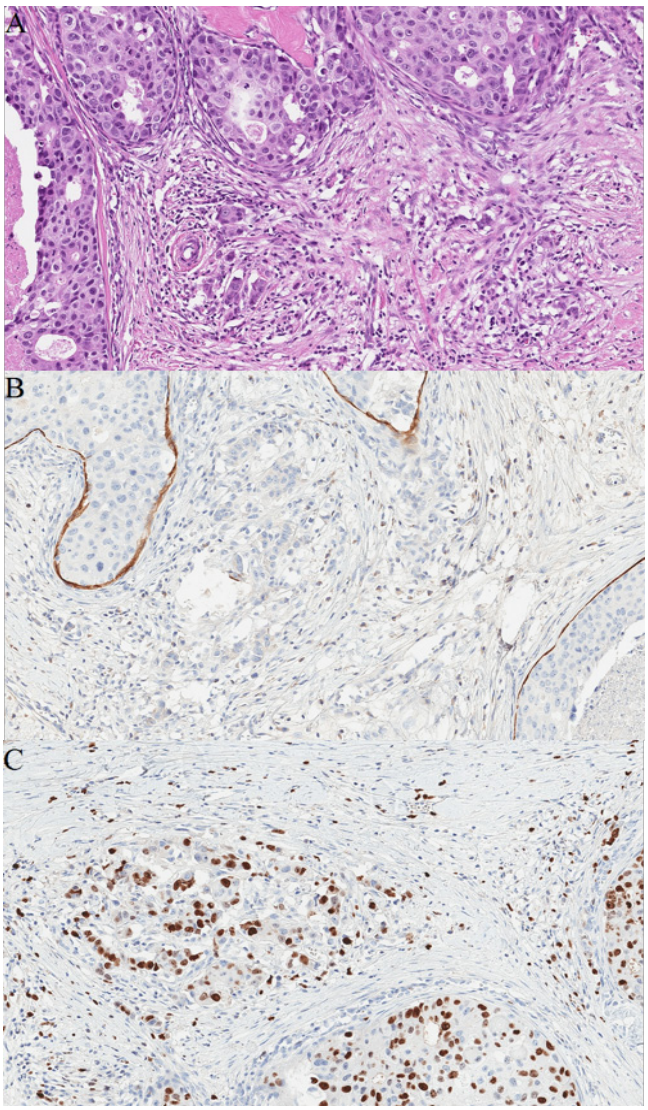

Figure 1: (A) HE, invasive ductal carcinoma and DCIS at 400x magnification showing infiltrative trabecules and separate cells of primary high grade ductal carcinoma (of no special type) in the breast tissue surrounded by intraductal solid type epithelial proliferation with high grade nuclear atypia and comedo necrosis. **(B)** CK5 at 400x magnification displays invasive epithelial structures lacking immunohistochemically CK5 positive myoepithelial layer seen in intraductal neoplasia nearby. **(C)** Ki67 at 400x magnification showing that proliferative index was about 50% of all primary carcinoma cells by immunohistochemical Ki67 positivity in nuclei.

was followed up at the outpatient clinic every month. Additionally, chest, abdomen and pelvis tomography showed no evidence of local and distant recurrence disease. After four months, she experienced headaches and dizziness for few weeks. Brain Magnetic Resonance Imaging (MRI) revealed a 17 x 19 mm polycyclic contour lesion in the left occipital lobe surrounded by perifocal edema (Figures 2). The clinical case was discussed at the tumor board and final decision was: craniotomy with tumor resection. Patient underwent complete tumor resection. Post-operative period was without complication. Final pathological examination revealed metastatic breast carcinoma with negative estrogen and progesterone receptors, HER2 positive receptors (Figure 3). She was treated with adjuvant chemotherapy and SRS radiotherapy (6 Gy×5 fractions for a total dose of 30 Gy) to the resection cavity. The patient is currently still on active treatment with this regime follow-up. No serious cardiotoxicity or neurotoxicity occurred.

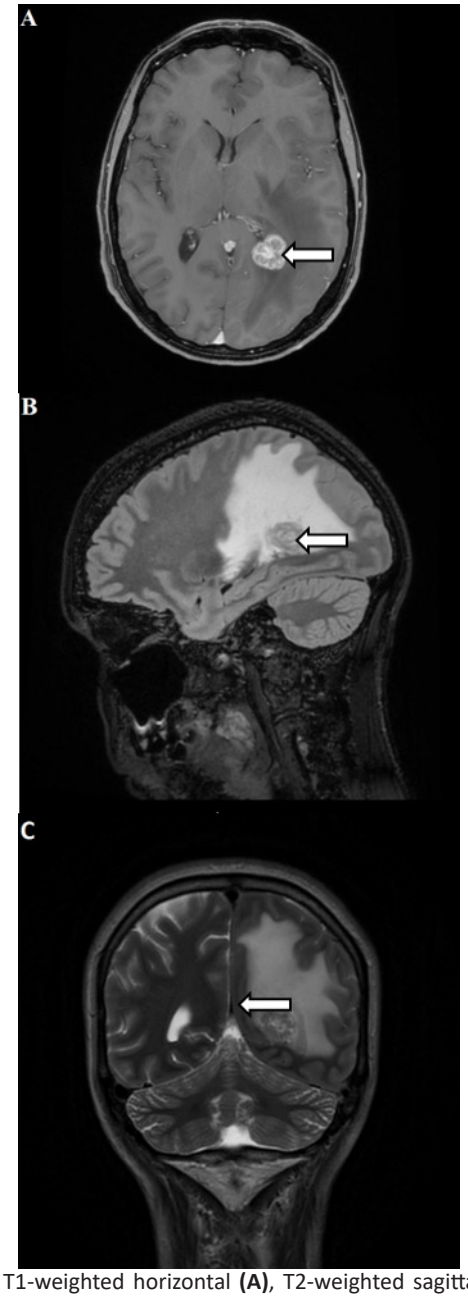

Figure 2: T1-weighted horizontal **(A)**, T2-weighted sagittal **(B)**, and T2-weighted coronal **(C)** MRI images of a 17 x 19 mm polycyclic contour lesion in the left occipital lobe, paraventricularly to the dorsal horn (arrow), with perifocal edema.

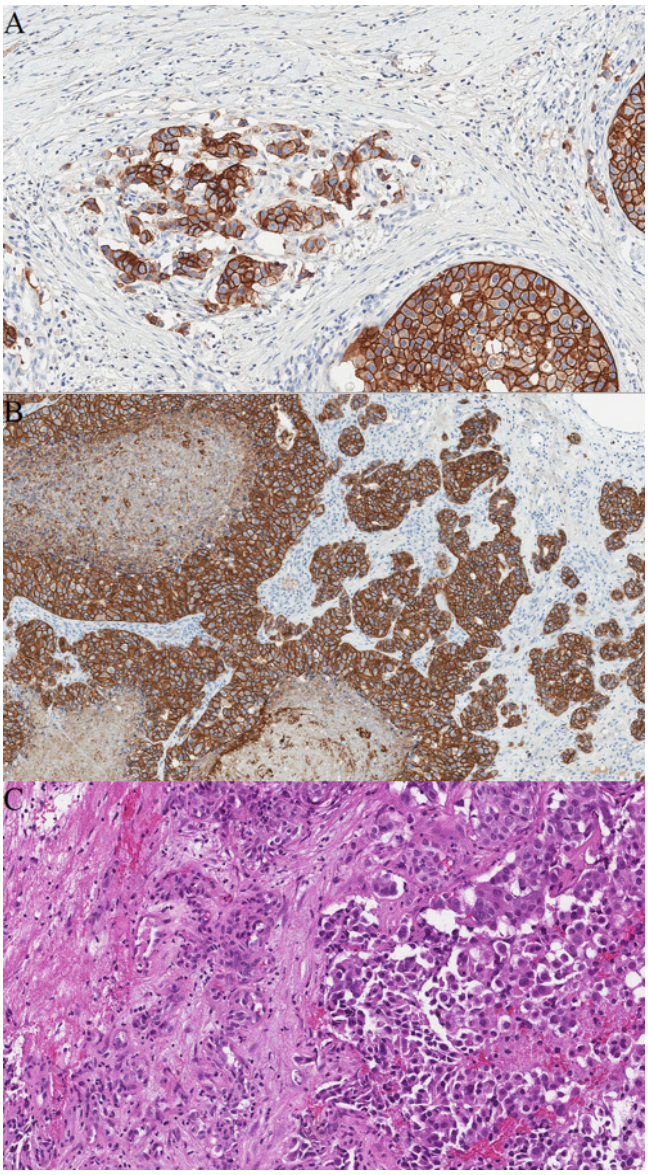

Figure 3: (A) HER2 positive at 400x magnification. **(B)** HER2 mts at 200x magnification displays immunohistochemical strong (3+) complete expression of HER2 receptor in 100% of invasive carcinoma cells. **(C)** HE mts at 400x magnification showing infiltrative nests of metastatic high grade ductal carcinoma (of no special type; right part of picture) in glial tissue.

Discussion

Overall, incidences of BCBM has been escalating in the last decade, due to increased detection of metastatic disease through advanced imaging techniques and improved overall survival. The incidence of breast cancer brain metastases (BCBM) has increased in the last few years, following improved patient survival rates and increased detection of metastatic disease through advanced imaging techniques [5]. However, overall survival (OS) in patients with HER2-positive BCBM was revealed as only 26.3 months [6]. In a recent meta-analysis [3], the pooled cumulative incidence of BM was 31% in patients with HER2-positive BC. The incidence of brain metastases per patient was 0.13 (95%CI: 0.09-0.20). Treatment of HER2-positive BCBM remains a challenge for oncologists. BM is managed with local therapies, including surgical resection, stereotactic radiosurgery, stereotactic radiotherapy, whole-brain

radiotherapy (WBRT), and systemic therapies, including chemotherapy and targeted therapy.

In this clinical case, we report a successful combined local and systemic approach for HER2-positive BCBM at 41 months of follow-up. To date, our patient had no signs of a relapsed tumor.

However, the role of surgery in this subset of patients with BM remains unclear. The possibility of surgical intervention is discussed during tumor board and is recommended only in cases with few lesions or large symptomatic lesions (≥3cm). Surgery followed by radiotherapy has been shown to improve OS compared to radiotherapy alone [7]. Patchell et al. [8] demonstrated that, in patients with a single BM, whole-brain radiotherapy after complete surgical resection reduced the rate of recurrence at both the initial metastatic site and other brain sites, and reduced death due to intracranial progression. In cases in which surgical resection is not feasible (multiple brain metastases) or the BM is single, small stereotactic radiosurgery (SRS) is the recommended approach. A multi-institutional prospective study [8,9] with 1194 patients showed that overall survival did not differ between the patients with two to four tumors and those with five to ten tumors. SRS might be a suitable alternative for patients with up to ten BM.

In the last decades, WBRT has played an important role in the palliative radiotherapy of patient with brain metastases (≥10). However, WBRT is associated with higher rates of cognitive deterioration [8,9]. New methods and techniques of brain irradiation have revealed mechanism and opportunities to prevent these side effects of WBRT. A phase III trial [9] showed that hippocampal avoidance (HA) using plus memantine better preserves cognitive function and patient-reported symptoms, with no difference in intracranial PFS and OS in patients with brain metastases. HA-WBRT should be considered a standard of care for patients with good performance status who plant to receive WBRT for brain metastases with no metastases in the HA region [9,10].

The management of HER2-positive BCBM systemic therapy has changed drastically in recent years. Since the introduction of trastuzumab, new alternative conjugates have been developed and demonstrated superior results. The CLEOPATRA trial [10] reported that the combination of pertuzumab, trastuzumab and docetaxel significantly improved overall survival among patients with HER2-positive metastatic breast cancer as compared with placebo, trastuzumab, and docetaxel. The median overall survival was 56.5 months in the group receiving the pertuzumab combination, as compared with 40.8 mpnths in the groups receiving the placebo combination. In the PERUSE trial [12], the safety profile of first-line pertuzumab combined with trastuzumab and standard taxane therapy for HER2-positive LR was consistent with the known safety profile of the individual agents and the results of the phase III CLEOPATRA trial.

The combination of trastuzumab, pertuzumab, and a taxane (THP) remains the preferred first-line neoadjuvant therapy in most scenarios [13]. The major problem with trastuzumab therapy is cardiotoxicity. However, cardiac dysfunction related to adjuvant trastuzumab is described in only 5% to 10% of patients in the clinical trials, most with recovery without any intervention [11,14]. Our patient underwent heart ultrasound every two cycles, and showed no evidence of cardiotoxicity. The current standard of adjuvant treatment in patients with ER/PR+ disease is completion of 1 year of HER2-targeted therapy, and at least 5 years of adjuvant endocrine therapy. In the KATHERINE trial, adjuvant treatment with T-DM1 resulted in a 50% lower risk of recurrence of invasive disease or death than adjuvant continuation of trastuzumab among patients with HER2-positive early breast cancer and residual invasive disease after completion of neoadjuvant chemotherapy plus HER2-targeted therapy [14]. However, recent randomized DESTINY-BREAST03 trial compared trastuzumab deruxtecan with T-DM1 in 524 patients with HER2-positive MBC previously treated with trastuzumab and a taxane. Trastuzumab deruxtecan showed a significant improvement in overall survival versus T-DM1, reducing the risk of death by approximately 36% in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab (with or without pertuzumab) and taxane [16]. In a phase 2 TUXEDO-1 trial [17], trastuzumab deruxtecan showed a high intracranial response rate of 73.3% in patients with active brain metastases from HER2-positive breast cancer, establishing this agent as the preferred second-line therapy.

Conclusion

The combination of local and systemic therapies was effective in reducing the recurrence of HER2-positive BCBM. To date, our patient has no signs of relapsed tumor. With a new anti-HER2 therapy agents, the overall survival of patients with BM are like to improve over time.

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