Incidental Diagnosis of Leptomeningeal Disease in Breast Cancer with Brain Metastases- a Case Report with Review of Literature

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Abstract: *Background***:** Breast cancer is the most common malignancy in women worldwide, with 2.3 million new cases and 6,70,000 deaths reported in 2022 (Globocan). Metastatic breast cancer affects up to 30% of patients, with brain metastases occurring in approximately 25%, especially among Human epidermal growth factor receptor 2 (HER2) positive subtypes. Leptomeningeal disease (LMD), the dissemination of tumor cells to the leptomeninges and cerebrospinal fluid (CSF), is an uncommon but devastating complication. Diagnosing LMD is often challenging due to nonspecific symptoms and overlapping imaging features with infectious or inflammatory conditions. CSF cytology remains the gold standard, though newer diagnostic techniques such as CSF-based circulating tumor DNA (ctDNA) are emerging.

*Case Presentation***:** We report a previously treated case of a 42-year-old premenopausal woman with HER2-positive, estrogen and progesterone receptor-negative, metastatic breast cancer, who presented with acute onset of altered sensorium, fever, and irritability. Magnetic Resonance Imaging (MRI) brain showed multiple enhancing lesions in the cerebral hemispheres, cerebellum, midbrain, and thalami, with surrounding edema. MR spectroscopy demonstrated reduced choline and elevated lipid-lactate peaks, initially suggesting an infective etiology, however, CSF cytology revealed malignant cells, with immunohistochemistry positive for GATA3 and PanCK, confirming leptomeningeal metastases of breast origin. She was planned for whole brain radiotherapy (WBRT) and intrathecal methotrexate.

*Conclusion***:** This case highlights the diagnostic challenges of LMD in HER2-positive breast cancer. Radiological and spectroscopy findings may mimic infectious processes, especially in tuberculosis-endemic regions. In ambiguous cases, reliance on CSF cytology is crucial, and adjunctive molecular diagnostics like ctDNA may further enhance diagnostic yield. Leptomeningeal metastasis, though underdiagnosed, has significant therapeutic implications. Newer HER2-directed intrathecal therapies, advanced radiotherapy techniques such as craniospinal irradiation with helical tomotherapy or proton therapy, and evolving strategies for CSF drug delivery offer promising avenues for treatment. A high index of suspicion and early CSF evaluation can lead to timely diagnosis and potentially improved survival outcomes in this difficult to treat subset.

Keywords: HER2-positive breast cancer; Leptomeningeal metastasis; Brain metastases; CSF cytology; MR spectroscopy; Intrathecal therapy; CNS involvement; ctDNA; Trastuzumab; Craniospinal irradiation.

INTRODUCTION

Breast cancer is a leading cancer in womenwith2.3 million patientsand 6.7 lakh deaths due to it according to Globocan 2022 [1] 20-30% of breast cancers are metastatic at presentation with the incidence of brain metastases being 25%.Out of the various molecular classifications of breast cancer the ones with Herceptin positive are amongst the most aggressive types [2,3]. The occurrence of brain metastasis has a positive correlation with Herceptin positive status to the tune of 94%;out of which 10% are symptomatic, while 29.6% patients are asymptomatic and found to have brain metastasis in their post mortem report [4,5]. Leptomeningeal involvement in brain metastases is relatively uncommon compared to parenchymal metastases, but is a very devastating complication [6]. Here, we report a case of 42 year-old female with locally advanced breast cancer, who presented with altered sensorium, fever and irritability, with an MRI spectroscopy revealing a diagnostic dilemma.

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CASE PRESENTATION

A 42year-old premenopausal female, a diagnosed case of Breast cancer with lung and mediastinal metastases with breast mass biopsy showing infiltrative ductal carcinoma Grade II, Estrogen Receptor and Progesterone Receptor status negative and Herceptin receptor status3 positive. Whole body Positron Emission Tomography and Computed Tomography (WB PET-CT) scan revealed 9.6x 9x12.3 cm mass in left breast (SUVmax-35.6) with multiple axillary and interpectoral and mediastinal lymph nodes and a solitary pulmonary nodule 1.5 cm (SUV max 11.5). Patient had already received 6 cycles of Injection Paclitaxel and Injection Trastuzumab from another hospital3 months ago. Patient then presented to our hospital with complaints of altered sensorium, irritability, fever and loss of appetite since 2 days. A contrast enhanced MRI Brain revealed multiple peripheral and nodular enhancing conglomerate lesions seen diffusely involving the bilateral cerebral and cerebellar hemispheres, midbrain, bilateral thalami and basal ganglia with adjacent oedema causing partial

ISSN: 1927-7210 / E-ISSN: 1927-7229/25

effacement of the bilateral lateral ventricles with minimal midline shift to the left side; largest lesion measuring 11x9mm in right parietal lobe (Figure **1**). Although brain metastasis were a more likely diagnosis in case of metastatic breast cancer, however the accompanying fever lead us to further investigate and to rule out infective etiology. MR Spectros copy showed reduced choline peak, increased lipid lactate peak suggestive of infective etiology–tuberculoma/ pyogenic infection (Figure **2**). However, Cerebrospinal fluid (CSF) cytology revealed presence of malignant cells

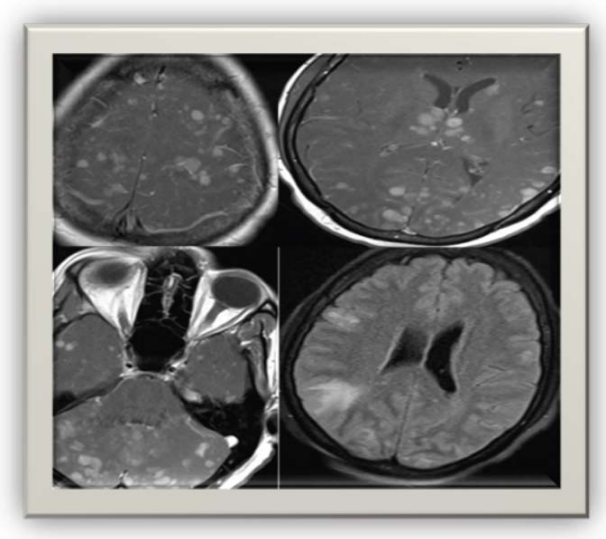

Figure 1: Contrast enhanced MRI film showing multiple peripheral and nodular enhancing conglomerate and similar lesions diffusely involving bilateral cerebral and cerebellar hemispheres, midbrain, bilateral thalamus and basal ganglia with adjacent edema with minimal shift towards left side, largest lesion measures 11x9mm in right parietal lobe.

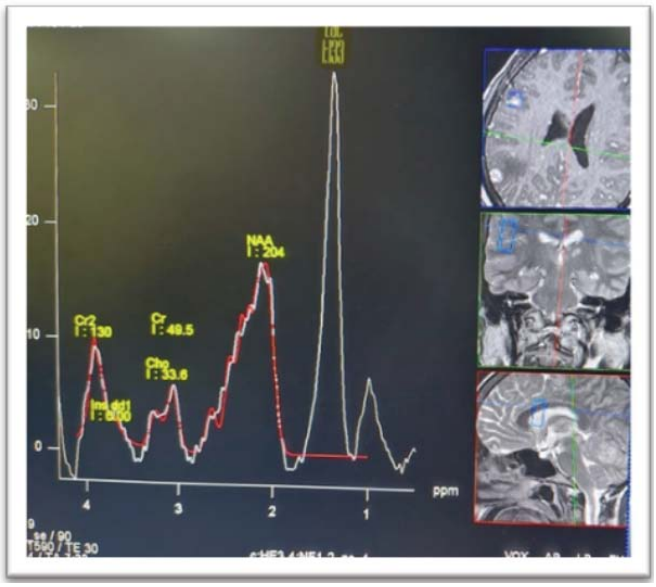

Figure 2: MR Spectroscopy showed reduced choline peak and increased lipid lactate peak.

and the cell block from the same revealed GATA3 and PANCK positivity (Figure **3**) which was suggestive Metastatic carcinoma of Breast origin. The patient was planned for intrathecal methotrexate and Whole Brain Radiotherapy but she did not receive further treatment at our center due to logistic issues.With varied and vague symptomatology leptomeningeal disease (LMD) can remain often undiagnosed and hence undertreated, unless a high clinical suspicion is kept. With no radiological features of LMD and an MR-spectroscopy showing likelihood of infection, the decision to pursue CSFcytology helped make an LMD diagnosis. We decided to report this case to highlight the importance of CSF cytology and treating the Cerebrospinal axisin such cases.

DISCUSSION

The increasing incidence of brain and meningeal metastases in breast cancer patients can be partly attributed to improved survival due to systemic therapies and the routine use of advanced neuroimaging. HER2-positive breast cancers, in particular, have a higher propensity for Central nervous system (CNS) metastases. Studies report that up to 25% of breast cancer patients develop brain metastases, and among HER2-positive patients, CNS involvement may occur in up to 50%, even during remission from systemic disease [4,7]. Brain metastases can be associated with leptomeningeal involvement although considerably less common than parenchymal metastases [6].

Most common imaging manifestation for brain metastases is presence of multiple intra-axial lesions. The amount of edema around these lesions can range from negligible to intense. Extra-axial mass lesions may arise as a result of metastasis to the dural lining or skull [8]. Leptomeningeal disease refers to spread of malignant cells to leptomeninges, Subarachnoid space and other CSF components. Leptomeningeal tumor deposits are formed by CSF dissemination of tumor in the brain parenchyma by means of rupture out of the subarachnoid space or vessels or if the metastases are into the choroid plexus. Owing to non-specific symptoms, leptomeningeal disease is often diagnosed late when symptoms become very severe [6]. Leptomeningeal spread may often remain asymptomatic and undiagnosed, with rates being as high as 20% in autopsy series [9].

In this case, a 42-year-old woman with metastatic HER2-positive breast cancer presented with acute neurological symptoms suggestive of some CNS

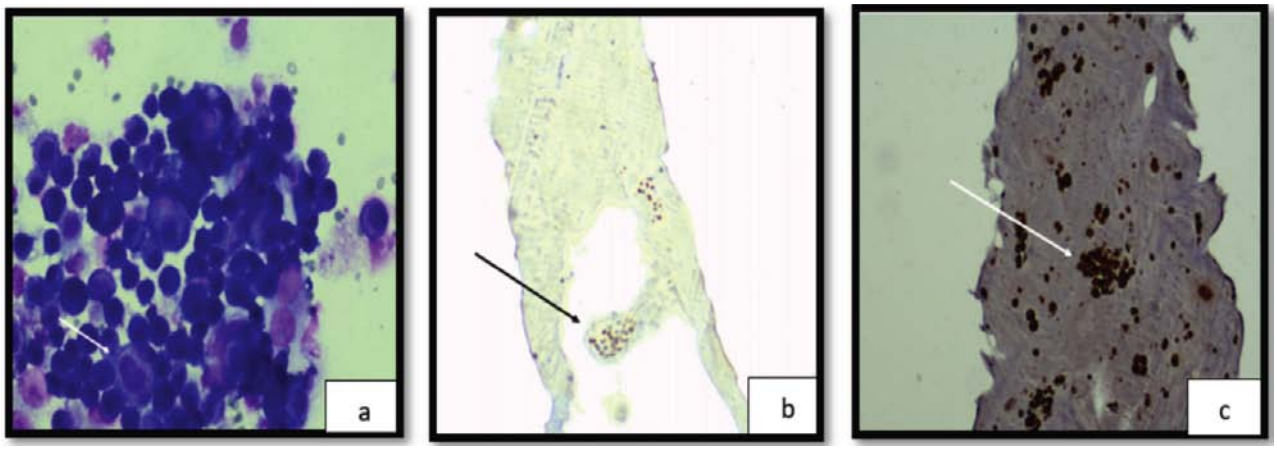

Figure 3: a- 40X high power field shows atypical cells with high N:C ratio, hyperchromatic nuclei and few binucleate forms. **b**- 10X field shoeing GATA 3 positivity. **c**- 10X field showing pan-cytokeratin positivity.

pathology. The MRI brain revealed multiple enhancing lesions, but MR spectroscopy suggested an infective etiology (reduced choline and increased lipid/lactate peaks). Such findings are typical for CNS infections such as tuberculoma or abscesses, especially in tuberculosis-endemic regions like India [10]. However, this case highlights that radiological features and even MR spectroscopy may be misleading, and should not replace histopathological confirmation in ambiguous cases.

The diagnosis of leptomeningeal spread is established by characteristic radiological signs or by CSF cytology. On CE-MRI brain, the gadolinium enhancement of the meninges can be confluent and sheet like or nodular with extension into the brain sulci, or along the cranial nerves or along the cauda equine [11,12]. CSF cytology (detection of malignant cells in CSF) is more sensitive than MRI for meningeal involvement in case of brain metastasis. CSF cytology positivity rate could be as high as 88.46% versus 65.38% for MRI positivity with improving sensitivity with repeated sampling [13] 6 out of 8 breast cancer patients with MRI findings suggestive of LMD had positive tumor cytology on CSF analysis, further underscoring the importance of lumbar puncture in such cases [14].

Circulating DNA (ctDNA) has emerged as a potential blood based marker for LMD diagnosis especially in scenarios where there are conflicting results between MRI and CSF cytology [15]. A few studies have investigated ultra-low pass whole-genome sequencing (ULP-WGS) on CSF-ctDNA for LMD diagnosis. ULP-WGS is a comparatively low-cost and rapid tool that relies on low coverage WGS and allows to estimate tumor content in ct DNA. It is also optimized to achieve high sensitivity even in low volume samples [16]. Modified fast aneuploidy screening test-sequencing system (mFAST-SeqS) method is an alternative to ULP-WGS, an equally fast and affordable technique to assess ctDNA fraction which employs selective amplification of long interspaced nuclear elements (LINE-1 sequences) Feasibility of mFAST-SeqS for LMD diagnosis and its sensitivity when compared to CSF cytology alone has been shown in some studies [18] liquid biopsy use should be incorporated into clinical trials involving breast cancer patients with brain metastases and LMD.

Whole brain radiotherapy has been the main stay of treatment of multiple brain metastases since 4-5 decades. Surgical excision and Stereotactic radiosurgery are recommended for limited brain metastases burden (Oligometastases). Systemic chemotherapy is known to have limited role in brain metastases due to an intact blood brain barrier(BBB) [17]. Because most chemotherapy agents used in the treatment of breast cancer either do not cross an intact BBB, or are pumped out of the CNS by phosphoglycoprotein in the endothelial cells in the BBB, they may not reach sufficient therapeutic levels to treat CNS metastases. However, in the setting of CNS lesions, the permeability of the BBB is likely increased via physical perturbation by tumors and by structural changes in tumormicrovessels that increase vascular permeability [20-22], including changes mediated by tumor secreted factors such as Vascular endothelial growth factor (VEGF) [18-21].

HER2-directed therapies, notably Trastuzumab, have demonstrated survival benefits in HER2- positive breast cancer patients with brain metastasis [22]. Newer agents like Trastuzumab emtansine (T-DM1)

and Tucatinib, particularly in combination with Capecitabine, have shown promising CNS activity in clinical trials [23,24].

For brain metastases with LMD, therapeutic options which can cater to the CSF, subarachnoid space and meninges in the spinal axis are needed. With challenges in diagnosis of LMD, treatment options are also based on limited data. WBRT with intrathecal therapy is associated with improved survival in LMD with Methotrexate been in use for the longest time [25]. Phase II trial results of Tucatinib in combination with Trastuzumab and Capecitabine showed superior median overall survival of 10 months and CNS progression time of 6.9 months for leptomeningeal metastasis in HER2positive breast cancer patients [26]. Intrathecal administration of newer drugs have also shown favourable outcomes. Intrathecal trastuzumab has been explored in studies for its safety and efficacy [27]. Innovative clinical trialsevaluating the combination of Intrathecal trastuzumab and Pertuzumab in combination with other systemic agents and /or radiotherapy offer encouraging new strategies for patient care [28].

WBRT and focal spine RT, is effective in symptom management, but does not generally improve overall survival with out-of-field failures being common [29]. Photon based craniospinal irradiation (CSI) for LMD from breast cancer has also been reported, but underutilised due to concerns of significant side effects [30]. Helical tomotherapy or volumetric-modulated arc therapy based CSI, allow for improved dosimetry and organ sparing [32]. Hypofractionated Proton beam therapy CSI owing to protons' negligible exit dose has been found to be feasible for patients with LMD from solid tumors [31].

Prophylactic cranial irradiation (PCI) has shown promise in reducing brain metastases and improving survival in mouse models [32]. Prospective randomised trials in this direction can help define if any, role of PCI in HER2 positive breast cancer.

CONCLUSION

LMD in HER2 positive breast cancer stands an underdiagnosed and thus undertreated entity. Keeping a high index of clinical suspicion, and pursuing a CSF cytology along with Ct-DNA analysis is vital in timely diagnosis and spinal axis directed treatment. With newer modalities of precision oncology available, in form of intrathecal therapies and precision photon-CSI and proton CSI, such patients can be offered a better progression free as well as overall survival.

LIST OF ABBREVIATIONS

HER2 = Human epidermal growth factor receptor 2

LMD = Leptomeningeal disease

CSF = Cerebrospinal fluid

ctDNA = Circulating tumor De-oxy ribo-nucleic acid

MRI = Magnetic resonance imaging

CNS = Central nervous system

ULP-WGS = Ultra-low pass whole-genome sequencing

mFAST-SeqS = Modified fast aneuploidy screening test-sequencing system

BBB = Blood brain barrier

VEGF = Vascular endothelial growth factor

WBRT = Whole brain radiotherapy

CSI = Craniospinal irradiation

PCI = Prophylactic cranial irradiation

DECLARATIONS

Ethics approval and consent to participate- Not applicable

Consent for publication- Written informed consent was obtained from the patient for publication of this case report and accompanying images.

The authors declare that there are no relevant financial or non-financial competing interests to report.

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Received on 20-08-2025 Accepted on 17-09-2025 Published on 20-10-2025

https://doi.org/10.30683/1927-7229.2025.14.08