Mirror Image or Molecular Mirage? Investigating Hormone Receptor Disconcordance in Breast Cancer Brain Metastases.

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Abstract

Breast cancer brain metastases (BCBM) are a significant clinical challenge, especially in aggressive subtypes like HER2-positive and triple-negative breast cancer. This review discusses hormone receptor discordance, it's existence and contributing factors, the role of the blood-brain barrier (BBB) in metastatic progression, and therapeutic modalities. While local treatments such as surgery and radiotherapy remain foundational, advances in systemic and immunotherapeutic approaches show promising potential. A deeper understanding of molecular mechanisms driving BCBM is essential to guide effective treatments and improve patient outcomes.

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Introduction

Breast cancer constitutes the second most prevalent origin of metastatic brain disease.[1] In approximately 12% of cases, the brain is identified as the initial site of distant metastasis. Clinical studies estimate that 10% to 16% of patients with advanced-stage breast cancer develop brain metastases during their disease course. The development of brain metastases has been associated with young age, and tumours that are estrogen receptor negative, Her-2+, >2 cm in diameter, node positive or of the basal phenotype. Hormone receptor profiling shows that 56% of tumours are estrogen receptor negative, 62% are progesterone receptor negative, 44% are HER[2] positive, and 28% are classified as triple-negative (TNBC). Hormone receptor (HR) status is not always static and may undergo alterations during the course of treatment or disease progression. Discordance occurs in HR expression between primary breast tumours and their corresponding metastases, with reported rates reaching up to 40% in matched tissue samples. The underlying mechanisms of HR status change are multifactorial. Proposed explanations include therapeutic selective pressure, clonal evolution, and intratumoral heterogeneity.

Review of Evidence:

A multicentric study from Poland by Duchnowska et al., investigated hormone receptor status in breast cancer brain metastases.[2] In one cohort utilizing an Allred score threshold of ≥3, conversion of estrogen receptor alpha (ERα) and progesterone receptor (PR) in brain metastases was observed in 29% of cases for both receptors, predominantly representing a shift from positive to negative expression. In contrast, HER2 conversion occurred in 14% of patients and displayed a more balanced bidirectional change. Notably, time to brain relapse, as well as the use of chemotherapy or trastuzumab, did not significantly influence receptor conversion. However, endocrine therapy was significantly associated with loss of ERα ($P = 0.021$) and PR ($P = 0.001$), suggesting a potential selective pressure exerted by hormonal treatments. Despite these changes, receptor conversion was found to have no significant impact on overall survival.

The process of metastasis is not solely governed by cellular behaviour but is also intricately influenced by specific genetic and molecular alterations. Identifying gene expression patterns associated with organ-specific metastasis is crucial for understanding tumour progression and developing targetted therapeutic strategies.

Khaitan et al., reports the role of KCNMA1 in breast cancer brain metastasis, global exon array and RT-PCR analyses revealed significantly higher expression of KCNMA1 in BCBM compared to primary tumours and metastases to other organs.[3] Immunohistochemistry confirmed increased expression and localization of the BKCa channel protein in metastatic tissues. Functional assays demonstrated that BKCa channel activity enhances tumor cell invasiveness and transendothelial migration, particularly in brain-tropic breast cancer cells (MDA-MB-361). Both genetic (siRNA-mediated knockdown) and pharmacologic inhibition of KCNMA1 significantly

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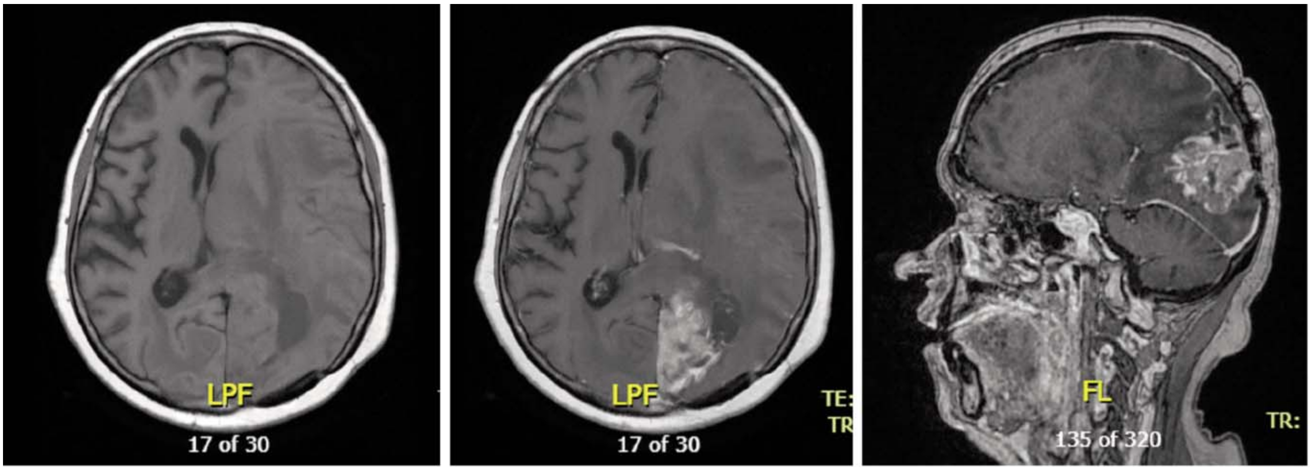

Figure-1: a,b,c. Pre-operative MRI TIWI axial pre contrast, axial post contrast and sagital post contrast images showing a solitary, large occipital metastatic breast cancer lesion.

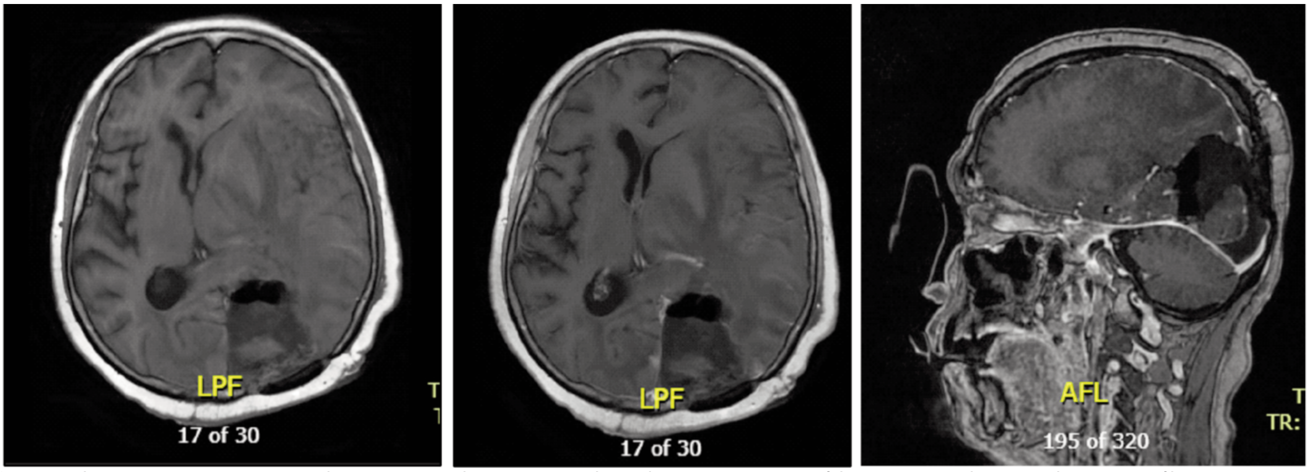

Figure-2: a,b,c. Post-operative MRI TIWI axial pre contrast, axial post contrast and sagital post contrast images of the same patient showing coplete excision of lesion.

attenuate these metastatic behaviours. This signifies BKCa channel expression as a biomarker for identifying breast cancers with high metastatic potential to the brain.

As outlined by Aversa et al., their study on central nervous system metastases (CNS-M) in breast cancer highlighted subtype-specific differences in the risk and prognosis of CNS involvement.[4] They found higher rates of CNS-M in HER2-positive subtypes, particularly pure HER2-positive and Luminal/HER2+, with the Luminal/HER2+ group showing the longest overall survival after CNS-M diagnosis. This emphasizes the importance of tumour subtype in predicting CNS metastasis and suggest that tailored management strategies could improve outcomes for affected patients.

Moreover, for metastasis breast cancer cells must first adhere to brain microvascular endothelial cells and penetrate the blood-brain barrier (BBB). Chhichholiya et al., in their comprehensive study on the BBB in breast cancer brain metastases (BCBM), explains how this disrupted BBB presents a unique therapeutic window, enabling the delivery of agents that would otherwise be excluded, and allowing for targetted interventions against metastatic tumour cells within the brain microenvironment.[5] Oncolytic virus therapy is a prime example that utilizes attenuated viruses that disrupts BBB to selectively infect and destroy tumour cells. Additional approaches under investigation include immune checkpoint inhibitors, mTOR-PI3K inhibitors, and emerging gene-editing technologies such as RNA interference (RNAi) and CRISPR/Cas9.

The management of brain metastases is complicated by several intrinsic challenges.[6] Historically, treatment of BCBM relied on local therapies due to the restrictive nature of the BBB. New agents like ANG1005 and etirinotecan pegol have shown promising results.[7] Traditional treatment approaches include surgery, whole brain radiation therapy (WBRT), and stereotactic radiosurgery (SRS). WBRT has long been a standard treatment for brain metastases. Patchel et al., have shown reduced intracranial recurrence when combined with surgery, despite no overall survival benefit.[8] (Figure 1, 2) Due to its associated toxicities, including somnolence and short-term memory impairment, WBRT is now primarily used for patients with multiple metastases and those with poor baseline performance status usually measured by the Karnofsky Performance Scale (KPS).

Immunotherapy is an emerging strategy for treating BCBM. Randomized controlled trials by Schmid et al., and Nanda et al., report that agents like pembrolizumab, nivolumab, and atezolizumab show promise, particularly in PD-L1–positive TNBC.[9] Ongoing trials are also exploring the synergistic potential of combining immunotherapy with radiation therapy due to its immune-priming effects.[10,11]

Conclusion

Breast cancer brain metastases continue to pose significant therapeutic challenges due to their heterogeneity and the protective nature of the BBB. Recent advances in systemic therapies and immunotherapy have begun to expand treatment possibilities beyond traditional local approaches. Improving outcomes for BCBM patients requires deeper insight into tumour biology, receptor changes, and treatment resistance. Personalized, molecularly guided therapies will be key to enhancing survival and quality of life.

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