



CASE REPORT

Solitary Intracranial Progression on Trastuzumab Deruxtecan Therapy in HER2-Positive Metastatic Breast Cancer: A Case Report

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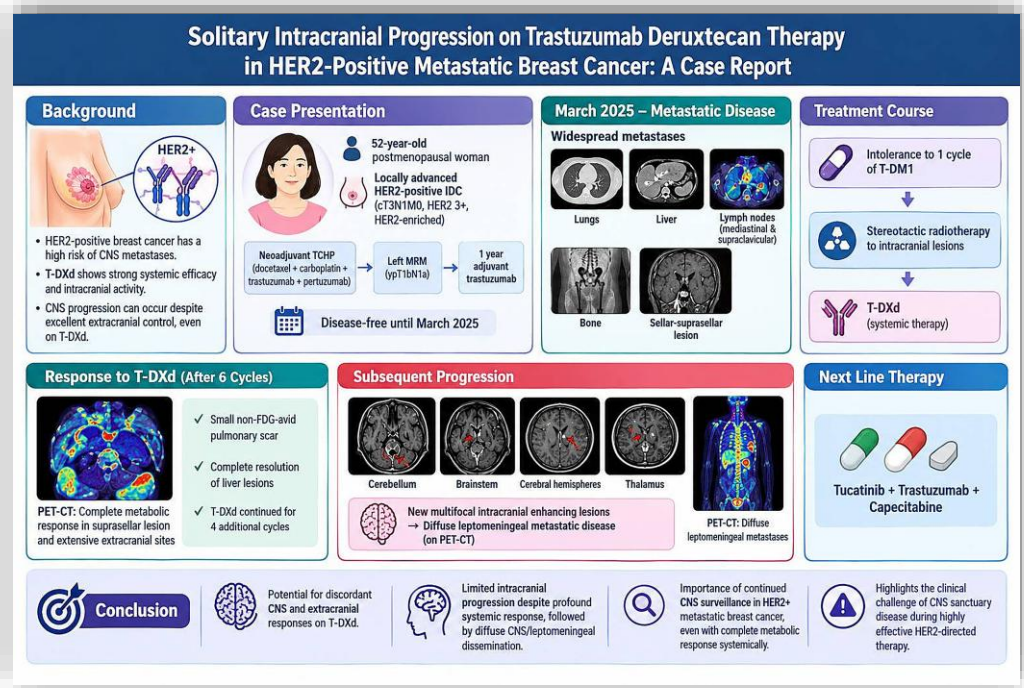
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Graphical Abstract

1. Abstract:

Background: Human epidermal growth factor receptor 2 (HER2)-positive breast cancer is characterized by a substantial risk of central nervous system (CNS) metastases. However newer agents such as Trastuzumab deruxtecan (T-DXd) has demonstrated substantial systemic efficacy and clinically meaningful intracranial activity in these patients. Nevertheless, CNS progression can occur despite excellent extracranial disease control even whilst on these agents.

Case presentation: We report the case of a 52-year-old postmenopausal woman with locally advanced, HER2-positive invasive ductal carcinoma of the left breast (cT3N1M0, HER2 3+, HER2-enriched phenotype). She received neoadjuvant docetaxel, carboplatin, trastuzumab, and pertuzumab, followed by left modified radical mastectomy, with residual ypT1bN1a disease. After completion of one year of adjuvant trastuzumab, she remained disease-free until March 2025, when imaging demonstrated widespread metastatic disease involving the lungs, liver, mediastinal and supraclavicular lymph nodes, bone, and a sellar-suprasellar lesion. After intolerance to one cycle of trastuzumab emtansine (T-DM1), multidisciplinary review led to stereotactic radiotherapy to the intracranial lesions followed by systemic T-DXd. She subsequently received T-DXd with marked systemic response. After six cycles, positron emission tomography-computed tomography (PET-CT) demonstrated a complete metabolic response in the suprasellar lesion and extensive extracranial metastatic sites, with only a small non-FDG-avid pulmonary scar and complete resolution of liver lesions. T-DXd was continued for four additional cycles. However, approximately the following period was characterized by new multifocal intracranial enhancing lesions involving the cerebellum, brainstem, cerebral hemispheres, and thalamus, with subsequent PET-CT demonstrating diffuse leptomeningeal metastatic disease. The patient was subsequently switched to tucatinib, trastuzumab, and capecitabine.

Conclusion: This case illustrates the potential for discordant CNS and extracranial responses during T-DXd therapy. Of particular interest is the development of limited intracranial progression despite a profound systemic response, followed by diffuse CNS/leptomeningeal dissemination. The case underscores the importance of continued CNS surveillance in HER2-positive metastatic breast cancer, even when systemic disease remains in complete metabolic response, and highlights the clinical challenge of CNS sanctuary disease during highly effective HER2-directed therapy.

2. Keywords:

HER2-positive Breast Cancer, Trastuzumab Deruxtecan, T-DXD, Brain Metastasis, Intracranial Progression,

Leptomeningeal Metastasis, CNS Sanctuary Disease, Sellar Metastasis, Stereotactic Radiotherapy.

3. Introduction:

HER2-positive breast cancer represents a biologically distinct subtype with an increased propensity for CNS dissemination. Improvements in HER2-directed systemic therapy have substantially prolonged survival, consequently, CNS metastases have become an increasingly important clinical problem. Although several HER2-directed agents demonstrate CNS activity, intracranial disease may exhibit differential sensitivity compared with extracranial disease, resulting in CNS progression despite systemic disease control [1].

Trastuzumab deruxtecan (T-DXd), an antibody-drug conjugate comprising a HER2-directed monoclonal antibody linked to a topoisomerase I inhibitor payload, has demonstrated substantial efficacy in HER2-positive metastatic breast cancer, including activity against brain metastases. Nevertheless, the CNS remains a clinically relevant site of disease progression.

We describe a patient with HER2-positive breast cancer who developed widespread metastatic recurrence followed by a limited intracranial progression pattern during T-DXd treatment. Importantly, the intracranial disease initially remained limited while the patient achieved a complete metabolic response at multiple extracranial sites. Subsequent progression evolved into multifocal CNS disease and diffuse leptomeningeal metastases. This case highlights the phenomenon of compartmental response and the potential for CNS sanctuary progression during otherwise highly effective HER2-directed therapy.

2. Case Presentation:

A 52-year-old postmenopausal woman was diagnosed in June 2022 with carcinoma of the left breast. Initial staging demonstrated a large primary tumor with regional nodal involvement, consistent with cT3N1M0 disease. Histopathological evaluation revealed invasive ductal carcinoma (IDC), with strong HER2 overexpression (HER2 3+) and a HER2-enriched molecular phenotype.

Initial Treatment:

The patient received neoadjuvant systemic therapy consisting of four cycles of docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP). Imaging demonstrated a partial response.

She subsequently underwent left modified radical mastectomy in October 2022. Histopathological examination demonstrated residual invasive disease measuring within the ypT1 category with nodal involvement, staged as ypT1bN1a.

Following surgery, she received two additional cycles of TCHP and subsequently completed one year of adjuvant trastuzumab in December 2023.

A PET-CT performed in February 2024 showed no definite evidence of metabolically active recurrent disease. There was mild soft tissue thickening along the right anterolateral chest wall without FDG avidity. A small rounded pulmonary nodule measuring approximately 6×6 mm in the superior segment of the right lower lobe demonstrated faint FDG uptake and was considered indeterminate.

The patient was therefore kept under surveillance.

Development of Metastatic Disease:

The disease-free interval was approximately 1 year and 3 months. In March 2025, PET-CT demonstrated extensive metabolically active metastatic disease.

A large FDG-avid mass measuring approximately 5.2×4 cm was identified in the right lower lobe of the lung, associated with bronchial cut-off. Multiple bilateral pulmonary nodules were also present, including a left lower-lobe nodule measuring approximately 1.1 cm.

Multiple hepatic metastases were identified, including a lesion in segment VIII measuring approximately 1.8×1.6 cm. FDG-avid mediastinal lymphadenopathy was present, with a dominant node measuring approximately 2.2×1.3 cm. Bilateral supraclavicular and level V cervical lymph nodes were also involved. FDG-avid osseous lesions were identified in the sacrum, acetabulum, and L2 vertebra.

Importantly, PET-CT also demonstrated a mildly FDG-avid nodular lesion in the sellar/suprasellar region with apparent pituitary enlargement.

Contrast-enhanced magnetic resonance imaging (CEMRI) of the brain in March 2025 demonstrated a $1.3 \times 1.7 \times 1.3$ cm enhancing sellar-suprasellar mass with hypothalamic involvement and contact with the optic chiasm, without definite compression. In the clinical context of disseminated HER2-positive breast cancer, metastatic disease was favored over a pituitary adenoma.

Initial HER2-Directed Treatment for Metastatic Disease:

The patient received one cycle of trastuzumab emtansine (T-DM1), which was poorly tolerated because of severe oral mucositis and odynophagia.

A repeat CEMRI of the brain in April 2025 demonstrated persistence of the sellar-suprasellar lesion and the development of a new 3-mm nodular enhancing lesion in the right cerebellar hemisphere.

Thus, although the intracranial disease burden was limited, there was radiological evidence of early intracranial progression.

Following multidisciplinary tumor board discussion, a strategy of local stereotactic radiation followed by continuation of systemic HER2-directed therapy was selected. Stereotactic body radiotherapy was delivered to the sellar/suprasellar and cerebellar lesions to a dose of 25 Gy in five fractions.

The patient was subsequently commenced on trastuzumab deruxtecan (T-DXd) at a dose of 300 mg every three weeks.

Response to Trastuzumab Deruxtecan:

The patient tolerated T-DXd well and received six cycles. PET-CT performed in July 2025 demonstrated a complete metabolic response in multiple disease sites. There was complete metabolic resolution of the previously identified suprasellar lesion, pulmonary disease, mediastinal lymphadenopathy, and osseous metastases. The previously identified hepatic lesions showed marked reduction, with complete resolution of the metabolically active liver lesions. A small residual pulmonary scar measuring approximately 2×1.8 cm was noted but was non-FDG avid. Thus, the patient achieved a deep systemic response to T-DXd, including resolution of the previously treated intracranial lesion. Given the excellent response and good tolerance, T-DXd was continued. The dose was subsequently administered at 200 mg every three weeks, and she received a further four cycles.

Subsequent intracranial progression and leptomeningeal disease.

Following continued T-DXd treatment, the patient experienced an episode of seizure. The event occurred the day after T-DXd administration and was clinically suspected to be related to hyperglycemia-induced seizure, antiepileptic therapy was initiated. EEG was subsequently normal.

CEMRI of the brain in December 2025, however, demonstrated a striking change in the pattern of CNS disease, with multiple small nodular enhancing lesions involving the cerebellum, brainstem, cerebral hemispheres, and thalamus.

PET-CT subsequently demonstrated findings consistent with diffuse leptomeningeal metastatic disease.

This represented a clinically important transition from initially limited intracranial disease to multifocal CNS and leptomeningeal dissemination, despite the preceding excellent extracranial response to T-DXd.

The patient was subsequently switched to a CNS-active HER2-directed regimen comprising tucatinib, trastuzumab, and capecitabine.

3. Discussion:

This case illustrates a clinically important phenomenon in HER2-positive metastatic breast cancer: discordant

intracranial and extracranial disease control during T-DXd therapy.

The patient initially presented with widespread metastatic disease involving the lungs, liver, lymph nodes, bone, and CNS. Following local stereotactic radiotherapy and initiation of T-DXd, she achieved a remarkable systemic response. The pulmonary, mediastinal nodal, osseous, and intracranial metabolic abnormalities showed complete or near-complete resolution. This degree of response is consistent with the substantial systemic and intracranial activity of T-DXd observed in HER2-positive metastatic breast cancer.

The unusual feature in this case was the subsequent evolution of CNS disease despite sustained systemic control. The initial intracranial progression was limited to the previously identified sellar-suprasellar lesion and a newly developed 3-mm cerebellar lesion. This represented limited or oligointracranial progression in the setting of otherwise widespread extracranial disease that subsequently demonstrated a profound response to T-DXd.

The sellar/suprasellar location is also notable. Pituitary and hypothalamic metastases from breast cancer are uncommon compared with more typical parenchymal brain metastases. In this patient, the lesion involved the sellar/suprasellar region with hypothalamic extension and contact with the optic chiasm. The radiological appearance and the context of disseminated metastatic disease favored metastatic involvement over a benign pituitary adenoma.

The decision to employ stereotactic radiotherapy followed by continuation of systemic HER2-directed treatment reflects an increasingly relevant clinical strategy for patients with limited intracranial progression and otherwise controlled systemic disease. Local ablative therapy may permit continuation of an effective systemic treatment rather than an immediate change of therapy, particularly when extracranial disease is responding.

The subsequent course, however, demonstrates the limitations of this strategy. After achieving a complete metabolic response at multiple extracranial sites, the patient developed multifocal intracranial lesions involving the cerebellum, brainstem, cerebral hemispheres, and thalamus, followed by diffuse leptomeningeal metastatic disease. This progression suggests a clinically distinct CNS disease compartment that was able to escape systemic disease control.

Several mechanisms may contribute to this phenomenon. The CNS has unique anatomical and pharmacokinetic characteristics, and drug penetration into the brain and cerebrospinal fluid may differ from exposure in extracranial tissues. In addition, intracranial metastases can display molecular heterogeneity relative to the primary tumor and extracranial metastases. These factors may

allow a resistant CNS subclone to emerge despite effective systemic suppression of HER2-positive disease elsewhere.

An important clinical implication is that excellent extracranial response should not necessarily be interpreted as evidence of equivalent intracranial disease control. In patients with known CNS involvement, serial brain MRI may therefore remain important even when systemic imaging demonstrates complete metabolic response.

The case also emphasizes the potential role of HER2-directed regimens with established CNS activity after CNS progression. Following the development of multifocal CNS and leptomeningeal disease, the patient was transitioned to tucatinib, trastuzumab, and capecitabine, a regimen with recognized activity in HER2-positive breast cancer with CNS involvement.

4. Conclusion:

This case highlights the possibility of limited early intracranial progression followed by diffuse CNS/leptomeningeal dissemination despite an otherwise excellent response to trastuzumab deruxtecan in HER2-positive metastatic breast cancer.

The case emphasizes three important clinical considerations. First, CNS disease may behave discordantly from extracranial metastases during effective HER2-directed therapy. Second, local stereotactic treatment can provide a strategy for managing limited intracranial progression while preserving an effective systemic therapy. Third, continued CNS surveillance should be considered in patients with a history of brain metastases even when extracranial disease demonstrates complete or near-complete response.

Further characterization of CNS-specific mechanisms of resistance to T-DXd and optimal surveillance strategies is warranted, particularly as patients with HER2-positive metastatic breast cancer experience increasingly prolonged systemic disease control.

5. Declarations:

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6. References:

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