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Clinically significant radiation necrosis following trastuzumab-deruxtecan and brain stereotactic radiosurgery: A case series in breast cancer patients

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ABSTRACT

An estimated 15% of breast cancers in the United States overexpress human epidermal growth factor receptor 2 (HER2), and patients with HER2+ breast cancer have an increased risk of developing brain metastases. The recent development of HER2-targeted agents, including trastuzumab deruxtecan (T-DXd), has resulted in improved systemic disease control, including disease metastasized to the brain. Because many patients with brain metastases have received both T-DXd and have also undergone brain stereotactic radiosurgery (SRS), it is important to explore the interaction of these treatment modalities. Here, we present two cases of clinically significant radiation necrosis (CSRN) occurring in patients with metastatic breast cancer with a treatment history including brain SRS and T-DXd. We also briefly describe two additional cases of CSRN in patients with the additional remote treatment history of trastuzumab emtansine (T-DM1) prior to T-DXd, as T-DM1 has also been reported to cause increased rates of CSRN in patients with HER2+ metastatic breast cancer with a history of SRS-treated brain metastases. While case reports and series have illustrated this phenomenon with T-DM1, no existing literature has described these findings with T-DXd. We describe these cases and review the potential etiologies for CSRN in this specific patient population, thus highlighting the need for a more thorough understanding of the potential adverse events caused by the intersection of treatment modalities, namely brain SRS and HER2-directed antibody-drug conjugates as the landscape of targeted therapies continues to evolve.

1. Introduction

An estimated 15% of breast cancers in the United States overexpress human epidermal growth factor receptor 2 (HER2) (Surveillance, epidemiology, and end results program, 2015). While brain metastases develop in up to 30% of patients with metastatic breast cancer overall, this can increase to 50% in patients with HER2+ breast cancer (Leyland-Jones, 2009). Given this increased propensity for central nervous system (CNS) disease in patients with HER2+ breast cancer, development of targeted agents directed at HER2 that are effective in the CNS are critical.

Trastuzumab-emtansine (T-DM1), an antibody-drug conjugate, was approved for metastatic HER2+ breast cancer following a phase III trial demonstrating improved median survival with T-DM1 (without increased risk for CNS progression) when compared with capecitabine/lapatinib (Verma, 2012; Krop et al., 2015). A second antibody-drug conjugate, trastuzumab deruxtecan (T-DXd), showed similar improvement in progression free and overall survival and more recently, received additional FDA approval for use in patients with metastatic HER2-low breast cancer (Modi, 2020; Modi et al., 2022). In addition, these two HER2 directed antibody drug conjugates have demonstrated CNS activity and improvement in survival for patients with brain metastases. The KAMILLA trial subgroup analysis in patients with HER2-positive disease and brain metastases showed an overall survival of 18 months with T-DM1 while the TUXEDO trial demonstrated a high intracranial response and a median progression-free survival of 15 months in the same population when treated with T-DXd (Montemurro, 2020; Bartsch et al., 2022). As such, NCCN guidelines list T-DM1 and T-DXd as recommended treatment regimens for breast cancer brain metastases (National Comprehensive Cancer Network (NCCN), 2023).

Abbreviations: HER2, human epidermal growth factor receptor 2; CNS, central nervous system; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; SRS, stereotactic radiosurgery; CSRN, clinically significant radiation necrosis; MRI, magnetic resonance imaging; ER, estrogen receptor; PR, progesterone receptor; THP, paclitaxel, trastuzumab, pertuzumab; WBRT, whole brain radiation therapy.

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In addition to these systemic therapies, stereotactic radiosurgery (SRS) remains an important component of local control in metastatic brain disease in patients with breast cancer. Local therapy, including surgery, radiosurgery, and radiation therapy, remains the primary modality for brain metastases treatment (Vogelbaum, 2022), and is frequently used prior to initiation of T-DM1 and T-DXd. A prior case series reported increased rates of clinically significant radiation necrosis (CSRN) in patients who received SRS for brain metastases within 15 months of undergoing T-DM1 therapy (Mitsuya et al., 2016). In this series, SRS was administered at a median of 8.5 days prior to T-DM1 infusion (range 3 days-449 days). In addition, a second case report outlined two cases of delayed CSRN associated with T-DM1 therapy (13–14 months following SRS) (Carlson et al., 2014).

To date, there is a paucity of reporting similar CSRN in patients who have received T-DXd following SRS. Herein, we review two cases of CSRN (based on symptoms and MRI findings) occurring in patients with metastatic breast cancer with a treatment history including SRS and T-DXd. We also briefly describe two additional cases of CSRN in patients with the additional remote treatment history of T-DM1 prior to T-DXd. For the purpose of this series, we consider CSRN to be synonymous with symptomatic radiation necrosis and indication for intervention.

2. Cases and methods

2.1. CSRN with T-DXd alone

Patient 1: A 62-year-old woman presented with a progressively worsening headache and vision changes. Magnetic resonance imaging (MRI) of the brain at that time revealed increased edema in the left occipital lobe concerning for radiation-associated necrosis.

This patient initially presented ten years prior with estrogen receptor (ER) negative, progesterone-receptor (PR) negative, HER2 positive T1aN0M0 breast cancer. She underwent bilateral mastectomy with no adjuvant therapy. She presented again six years later with imaging evidence of likely metastatic disease (liver, bone, and lung) and poorly differentiated carcinoma (ER negative, PR negative, HER2 positive) was demonstrated on liver biopsy.

She received six cycles of THP (paclitaxel, trastuzumab, pertuzumab), followed by seven months of maintenance HP. At that time, MRI of the brain revealed likely pituitary metastasis, and this was treated with SRS. Subsequent systemic therapy included capecitabine and tucatinib. One year after the identification of pituitary metastasis, new brain lesions were noted, specifically in both cerebellar hemispheres and the left occipital lobe. Given the location of these lesions, leptomeningeal disease was a concern, and she received intrathecal Herceptin for one year despite negative cerebrospinal fluid cytology. During that time, she also received SRS to six brain lesions.

Approximately three years following metastatic diagnosis and five months after most recent SRS, the patient received her first dose of T-DXd for progression of disease in the brain. Three months after the initiation of T-DXd, the patient presented for emergency care as noted above for headache and vision changes (Fig. 1). The increased left occipital lobe edema was managed with dexamethasone and T-DXd was held for a period of three months. Her headaches and vision changes improved during this time and MRI of the brain also showed reduced edema. The patient re-started T-DXd and received an additional 6 cycles without further neurological concerns.

Patient 2: A 46-year-old women presented with diplopia and occasional headaches. An MRI of the brain was performed at this time and showed extensive vasogenic edema within the bilateral frontal lobes (Fig. 2). She was started on dexamethasone for presumed radiation-associated necrosis and symptoms diplopia began to resolve.

This patient was initially diagnosed with ER positive, PR positive, HER2 positive T1N0M0 breast cancer. Initial management included bilateral mastectomies, as per patient preference, followed by adjuvant docetaxel, carboplatin, and trastuzumab with trastuzumab extended for one year total and approximately one year of adjuvant tamoxifen and one year of adjuvant anastrozole.

Five years after initial diagnosis, the patient developed back pain with imaging findings of a T8 compression fracture. Bone biopsy at this site showed metastatic breast cancer, ER positive, PR positive and HER2 positive. With no other findings of metastatic disease, she underwent radiofrequency ablation of the T8 site. Following, this, she began treatment with zoledronic acid along with THP. With progression of disease five months later, she transitioned to fulvestrant, trastuzumab and pertuzumab. Surveillance MRI approximately one year later showed multiple brain metastasis, prompting whole brain radiation therapy (WBRT). At that time, the patient also began systemic therapy with capecitabine, tucatinib, and trastuzumab.

Seven months following the completion of WBRT, the patient underwent SRS for progressive brain metastatic lesions; this was repeated approximately one year later. Her next line of systemic therapy was T-DXd, initiated one month following her most recent course of SRS. Five months following this, the patient began to report her new diplopia, resulting in the brain MRI outlined above. T-DXd was held and not re-started.

2.2. CSRN with both T-DMI and T-DXd

Two other patients were noted to have CSRN following T-DXd initiation, at fifteen and five months, respectively. Of note, these patients also received T-DM1 as a prior line of therapy (twenty-eight and forty-three months prior to findings of RN). Case reports and series have outlined the increased rates of CSRN among patients with breast cancer treated with T-DM1 having received SRS within 15 months of T-DM1 initiation. The two cases reported here demonstrate CSRN outside of that previously reported timeframe. Both patients received dexamethasone for symptoms of weakness and gait abnormalities and T-DXd was

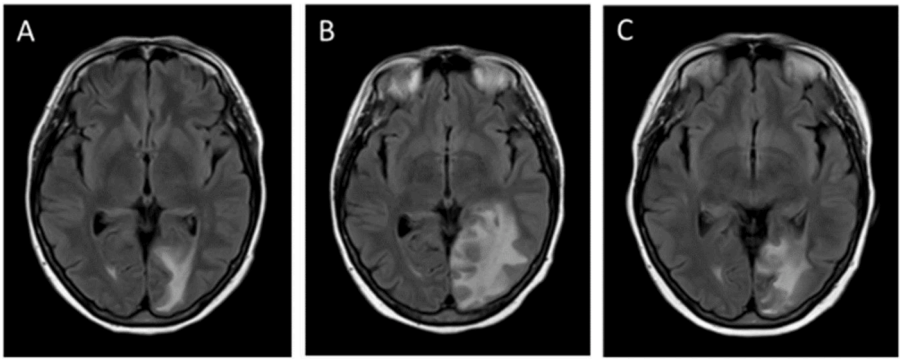

Fig. 1. (A) Axial FLAIR imaging 25 days prior to T-DXd initiation; (B) 2.5 months after initiation with worsening vasogenic edema in the left occipital region, now extending along the medial temporal lobe and periarterial white matter with worsening mass effect and (C) 3 months after T-DXd discontinuation.

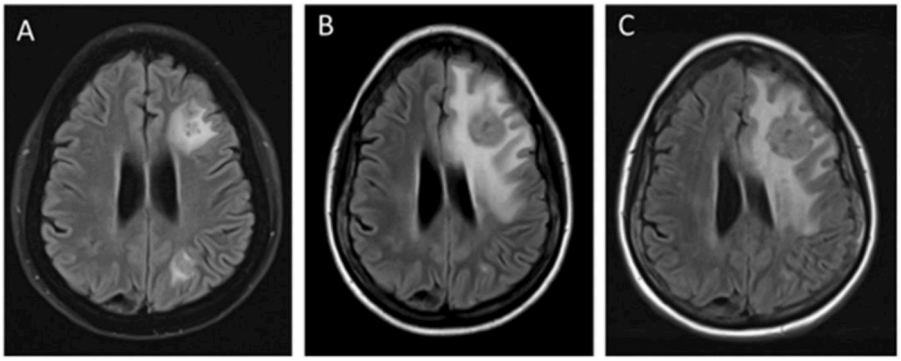

Fig. 2. (A) Axial FLAIR imaging 1 month prior to T-DXd initiation; (B) 5.5 months after initiation with worsening vasogenic edema surrounding the largest left frontal lobe lesion, resulting in mild subfalcine herniation of the rostral cingulate gyrus and (C) 2 months after T-DXd discontinuation with stable findings.

not re-started in either case, due to progression of disease for one patient and enrollment in hospice care for another patient.

For perspective, during the time in which the four patients described developed clinically significant radiation necrosis, a total of eleven patients with metastatic breast cancer and brain metastases were treated with SRS followed by T-DXd at our institution. Patients were identified based on an initial retrospective search for a T-DXd treatment plan in the medical record from 2016 to 2022. 128 patients were identified initially and patients with brain metastases and SRS preceding T-DXd were included based on documentation and imaging review. Of the eleven patients meeting this criteria, nine patients had received SRS within two years of starting T-DXd therapy. Two patients developed CSRN within six months of T-DXd initiation and two additional patients experienced CSRN in the setting of T-DM1 followed by T-DXd. This cohort of eleven patients did have differences in their SRS dosing, number of SRS courses, number and size of lesions treated and history of WBRT, all of which are additional known risk factors for CSRN. These characteristics are outlined in Table 1 with a specific focus on SRS received within a two-year period of T-DXd initiation.

3. Discussion

Clinically significant radiation necrosis is a challenging entity to both identify and manage in survivors of SRS for brain metastases. SRS dose recommendations have largely stemmed from the Radiation Therapy Oncology Group (RTOG) dose-escalation trial that sought to reduce rates of radiation necrosis, reporting a 2-year rate of 11% for radiation necrosis, which is dependent on radiation dose delivered and target volume irradiated (Shaw et al., 2000). It is important to note that the diagnosis of radiation necrosis itself is challenging as its features overlap with metastatic disease progression or recurrence (Detsky et al., 2017). This is especially true with the most used imaging modality, MRI. If feasible, confirmation of a diagnosis of radiation necrosis can be furthered with MR spectroscopy or even pathological assessment, although invasive (Muto et al., 2018; Szeifert et al., 2006). In the presence or absence of advanced imaging or tissue diagnosis, a multidisciplinary discussion with medical oncology, radiation oncology and surgical oncology is needed to address the potential of radiation necrosis or metastatic progression as treatment options greatly differ.

In our series, four of eleven patients (33%) with metastatic breast cancer who received T-DXd following SRS did develop clinically significant radiation necrosis, or symptomatic radiation necrosis requiring intervention. Due to the limitations of this report's retrospective nature and the small sample size, no conclusions can be drawn that the incidence of CSRN is increased compared to the RTOG rate of 11%. We also note that this study population of eleven patients is heterogeneous both in terms of prior systemic therapy and in terms of SRS characteristics. However, our experience parallels other case series and reports that demonstrate a similar phenomenon in breast cancer patients who received SRS for brain metastases, followed by systemic T-DM1 therapy. In one series, four of seven patients developed clinically significant radiation necrosis (57%) with T-DM1 initiation at a range of three days to 15 months post-SRS (Carlson et al., 2014).

To our knowledge, no similar data or reports have described CSRN following SRS and T-DXd treatment. T-DXd is an antibody drug conjugate that consists of a humanized HER2-directed monoclonal antibody and a topoisomerase-I inhibitor with high membrane permeability (Center For Drug Evaluation and Research, 2022). Furthermore, the drug:antibody ratio in T-DXd is higher than the ratio seen with T-DMI and previous studies have demonstrated disease activity for T-DXd in patients with progression of disease on T-DMI (Ogitani et al., 2016). T-DXd has shown impressive activity in the CNS with an intracranial response rate of 73.3%. Given this, it is possible that the CSRN described following T-DXd and SRS is a result of increased drug concentration crossing the blood brain barrier and increased ability to target HER2 positive disease, including that seen in the brain. A higher payload

Table 1
Patient characteristics of eleven total patients with brain metastases and SRS preceding T-DXd as identified on documentation and imaging review.

Patient	Age (years)	CSRN (Y/N)	History of WBRT (Y/N)	Total no. SRS courses	No. SRS courses within two years of T-DXd start	No. treated lesions within two-year period (per course)	Max. lesion size (mm) within two-year period (per course)	SRS dose (Gy) within two-year period (per course)	Prior T-DM1 therapy (Y/N)
1	62	Y	N	2	2	5, 6	9, 10	22, 22	N
2	46	Y	Y	2	2	5, 4	13, 10	22, 20	N
3	63	Y	N	4	2	2,1	11, 7	22, 22	Y
4	59	Y	Y	2	0	0	NA	NA	Y
5	62	N	N	2	1	1	14, 12	22, 20	N
6	51	N	N	1	0	0	NA	NA	N
7	42	N	Y	1	1	2	24	18	N
8	49	N	Y	1	1	2	7	20	N
9	50	N	N	3	1	1	28	20	N
10	61	N	N	2	1	5	5	20	N
11	61	N	Y	2	2	2, 1	10, 7	20, 22	N

membrane permeability also allows for a cytotoxic effect on tumor cells near the targeted cells, regardless of HER2 expression, known as a "cytotoxic bystander effect (Indini et al., 30)." This "bystander effect" may be responsible for an overall increase in cytokine release and resultant cerebral edema contributing to radiation necrosis following T-DXd.

4. Conclusion

We describe four total cases of CSRN in patients with HER2+ breast cancer and brain metastases who have undergone SRS followed by T-DXd. This patient cohort is heterogenous in terms of prior therapies received and in two cases, prior therapy did include T-DMI (although greater than 24 months prior to development of CSRN). The four patients described developed CSRN within 15 months of T-DXd administration with a range of 2.5–15 months, suggesting a correlation.

SRS has remained a mainstay in the management of metastatic brain lesions in patients with breast cancer. More recently, targeted agents, specifically for HER2+ metastatic breast cancer have demonstrated clinically meaningful benefit for patients; specifically, T-DXd efficacy was shown in the TUXEDO-1 trial in which T-DXd yielded intracranial responses in 73.3% of the treatment population and showed a median progression-free survival of 14 months (Bartsch et al., 2022). With increased survival in this patient population, it is necessary to further explore the interaction between SRS and targeted agents as their usage will certainly overlap. It may be that a "wash-out period" between SRS and T-DXd is needed to prevent CSRN, presenting a subject for further investigation.

NCCN guidelines state that a trial of systemic therapy with good CNS penetration (such as T-DXd) "may be considered" in patients with small asymptomatic brain metastases, prior to radiotherapy. As further evidence accumulates regarding the risk of CSRN in patients who receive HER2 directed antibody-drug conjugates after brain SRS, this approach may become the preferred standard. If so, subsequent salvage therapy choices may become further complicated, highlighting the necessity of multidisciplinary discussion and decision making (Spałek and Mandat, 2022).

Patient consent form

The authors declare that they have obtained consent from the patients discussed.

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Victoria Wytiaz: Methodology, Data curation, Writing – original draft. **Anne Schott:** Conceptualization, Resources, Writing – review & editing. **Aki Morikawa:** Resources, Writing – review & editing. **Michelle M. Kim:** Writing – review & editing.

Declaration of Competing Interest

None.

References

Surveillance, epidemiology, and end results program. Cancer stat facts: female breast cancer subtypes. 2015 2019. Available from: https://seer.cancer.gov/statfacts/html/breast-subtypes.html.

Leyland-Jones, B, 2009. Human epidermal growth factor receptor 2-positive breast cancer and central nervous system metastases. J. Clin. Oncol. 27 (31), 5278–5286. https://doi.org/10.1200/JCO.2008.19.8481. Epub 2009 Sep 21. PMID: 19770385.

Verma, 2012. Trastuzumab emtansine for HER2-positive advanced breast cancer. N. Engl. J. Med. 367, 1783–1791.

Krop, I.E., et al., 2015. Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA. Ann. Oncol. 26 (1), 113–119.

Modi, 2020. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. N. Engl. J. Med. 382, 610–621.

Modi, S., et al., 2022. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. N. Engl. J. Med. 387, 9–20.

Montemurro, 2020. Trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer and brain metastases: exploratory final analysis of cohort 1 from KAMILLA, a single-arm phase IIIb clinical trial. Ann. Oncol. 31 (10), 1350–1358.

Bartsch, R., Berghoff, A.S., Furtner, J., et al., 2022. Trastuzumab deruxtecan in HER2-positive breast cancer with brain metastases: a single-arm, phase 2 trial. Nat. Med. 28, 1840–1847. https://doi.org/10.1038/s41591-022-01935-8.

National Comprehensive Cancer Network (NCCN). Central nervous system cancers. Version 1.2023. March 24, 2023. Brain Metastasesa: Systemic Therapy. Available from https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf.

Vogelbaum, 2022. Treatment for brain metastases: ASCO-SNO-ASTRO guideline. J. Clin. Oncol. 40 (5), 492–516.

Mitsuya, K., et al., 2016. Expansive hematoma in delayed cerebral radiation necrosis in patients treated with T-DM1: a report of two cases. BMC Cancer 16, 391.

Carlson, Julie A., et al., 2014. Trastuzumab emtansine and stereotactic radiosurgery: an unexpected increase in clinically significant brain edema. Neurooncology 16 (7), 1006–1009.

Shaw, E., Scott, C., Souhami, L., et al., 2000. Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: final report of RTOG protocol 90–05. Int. J. Radiat. Oncol. Biol. Phys. 47 (2), 291–298.

Detsky, J.S., Keith, J., Conklin, J., Symons, S., Myrehaug, S., Sahgal, A., et al., 2017. Differentiating radiation necrosis from tumor progression in brain metastases treated with stereotactic radiotherapy: utility of intravoxel incoherent motion perfusion MRI and correlation with histopathology. J. Neurooncol. 134, 433–441.

Muto, M., Frauenfelder, G., Senese, R., Zeccolini, F., Schena, E., Giurazza, F., et al., 2018. Dynamic susceptibility contrast (DSC) perfusion MRI in differential diagnosis between radionecrosis and neoangiogenesis in cerebral metastases using rCBV, rCBF and K2. Radiol. Med. 123, 545–552.

Szeifert, G.T., Atteberry, D.S., Kondziolka, D., Levivier, M., Lunsford, L.D., 2006. Cerebral metastases pathology after radiosurgery: a multicenter study. Cancer 106, 2672–2681.

Center For Drug Evaluation and Research, 2022. Application Number 761139Orig1s000, Product Quality Review(s). Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761139Orig1s000ChemR.pdf.

Ogitani, Y., et al., 2016. DS-8201a, a novel HER2-targeting ADC with a novel DNA topoisomerase I inhibitor, demonstrates a promising antitumor efficacy with differentiation from T-DM1. Clin. Cancer Res. 22, 5097–5108.

Indini, A., Rijavec, E., Grossi, F., 2021. Trastuzumab Deruxtecan: changing the destiny of HER2 expressing solid tumors. Int. J. Mol. Sci. 22 (9), 4774. https://doi.org/10.3390/ijms22094774. PMID: 33946310; PMCID: PMC8125530.

Spałek, M.J., Mandat, T., 2022. Salvage treatment for progressive brain metastases in breast cancer. Cancers 14 (4), 1096.