

Case Report

Multidisciplinary Care of a Large Brain Metastasis in a Patient with Hormone-Receptor-Positive Breast Cancer with Ataxia-Telangiectasia Mutation

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ABSTRACT

Poly (adenosine diphosphate-ribose) polymerase inhibitors (PARP)i are emerging as standard oncology treatments in various tumor types. The indications will expand as PARPi are being investigated in various breast cancer subtypes. Currently, except for *BRCA1/2* mutation carriers with human epidermal growth factor receptor 2 (HER2)-negative breast cancer, there is inadequate identification of predictive biomarkers of response. We present a 57-year-old woman with metastatic breast cancer, hormone-receptor-positive, HER2 negative with a germline ataxia-telangiectasia mutation with a large brain metastasis with clinical benefit to talazoparib. This case report exemplifies the importance of the multidisciplinary management of patients with brain metastases and personalized biomarker selected treatment.

Keywords: brain metastasis, breast cancer, ataxia-telangiectasia mutation (ATM), PARPi, precision medicine

INTRODUCTION

Approximately 10–30% of patients with metastatic breast cancer will develop brain metastases during their disease.^[1,2] Based on the number, size, and location of the brain metastases, primary treatment relies on surgical resection or radiation therapy (stereotactic radiosurgery

or whole-brain radiation therapy [WBRT]).^[3–5] Here we present a report on the multidisciplinary approach of a patient with metastatic hormone-receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer with ataxia-telangiectasia mutation (ATM) loss and a large brain metastasis. The patient provided written informed consent before initiation of treatment

and for publication of the data contained in this case report.

CASE SUMMARY

A 57-year-old woman was diagnosed in August 2005 with stage IIb invasive ductal carcinoma of the left breast, estrogen and progesterone receptor positive (estrogen receptor, 95%; progesterone receptor, 90%), HER2 negative. She was treated surgically with a left mastectomy and left axillary lymph node dissection (pT2N1M0) along with breast reconstruction, followed by anthracycline and taxane-based adjuvant chemotherapy, regional chest wall radiation, and was not compliant with adjuvant tamoxifen.

In December 2006, she was diagnosed with biopsy-proven left iliac bone metastasis of her known breast cancer. She was started on therapy with anastrozole and zoledronic acid until May 2012, when a bone scan showed new metastases in the left iliac bone and fifth lumbar vertebra (L5). She received palliative radiation to these two areas and continued anastrozole with the addition of fulvestrant.

Genetic testing for germline mutations in breast cancer genes (*BRCA1* and *BRCA2*) was negative. For tumor genetic analysis, DNA was extracted from formalin-fixed, paraffin-embedded analysis tumor samples. Tissue genetic analysis was conducted by next-generation sequencing using the Foundation One platform, which includes all genes known to be somatically altered in solid human tumors that are validated as targets for therapy, either approved or in clinical trials and/or that are unambiguous drivers of oncogenesis based on current knowledge. The current assay interrogates 315 genes and introns of 28 genes involved in rearrangements.

In March 2014, a chest computed tomography (CT) showed lung and lymph node metastases resulting in a therapy change to exemestane and everolimus until January 2015. Genomic testing (Foundation One platform) on tumor tissue showed several genomic alterations, including *ATM* loss (Table 1). The patient received several other treatments, including tamoxifen, capecitabine, eribulin, palbociclib, and fulvestrant until August 2017.

In October 2017, she was enrolled in a cisplatin-based chemotherapy phase I clinical trial that she tolerated well initially. In July 2018, she presented with hearing loss and bilateral tinnitus. A CT head without contrast showed no acute intracranial findings. She reported other intermittent neurological complaints, such as occasional headaches, difficulties with word-finding and writing, decreased short-term memory, and impaired attention. However, these were considered possibly chemotherapy-related in the absence of a focal neurologic deficit and the intermittent nature of the neurological symptoms.

Table 1. Next-generation sequencing genomic profile by Foundation One (as of January 2015)

Genomic Profile^a

CCND1 amplification
ATM loss exons 57–63
MCL1 amplification
NOTCH2 p.A3F
EMSY amplification
ESR1 p.Y537S
FGF19 amplification
FGF3 amplification
FGF4 amplification

^aGene symbols and full gene name as approved by the HUGO Gene Nomenclature Committee.

ATM: ATM serine/threonine kinase; *CCND1*: cyclin D; *EMSY*: BRCA2 (DNA repair associated) interacting transcriptional repressor; *ERBB2*: erythroblastic oncogene; *ESR1*: estrogen receptor 1; *FGF3*: fibroblast growth factor 3; *FGF4*: fibroblast growth factor 4; *FGF19*: fibroblast growth factor 19; *MCL1*: myeloid cell leukemia 1; *NOTCH2*: neurogenic locus notch homolog protein 2.

In March 2019, an 18F-2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography-CT (PET-CT) showed a new pericardial metastasis, which resulted in the discontinuation of the phase I trial. Given that the patient's sister was found to have an *ATM* del exons 56–62 germline mutation and the presence of *ATM* loss on the Foundation One report of our patient, the patient underwent repeat genetic counseling and testing in January 2019. Her results were positive for an *ATM* gene mutation (del exons 56–62).

In April 2019, she started a clinical trial with talazoparib, a poly-ADP-ribose polymerase inhibitor (PARPi) because of the *ATM* loss (ClinicalTrials.gov Identifier: NCT02286687). Her previously reported neurologic symptoms had resolved shortly after starting treatment with the PARPi. She had an overall stable disease until January 2020, when a PET-CT showed new lung metastases and suggested a possible brain metastasis. A brain magnetic resonance imaging (MRI) scan revealed a 3.8 × 2.9-cm well-demarcated T2 hyperintense lesion with intrinsic T1 hyperintensity involving the left posterior medial and inferior temporal gyri with an internal 1.1 × 0.9 cm enhancing nodule (Fig. 1A). In addition, a 1-cm-thick hemosiderin ring was seen in the left cerebellum and a 0.9-cm nonenhancing, T2 hyperintense, well-demarcated lesion in the left posterior parietal lobe (Supplemental Fig. 1).

The patient was referred to the Multidisciplinary Brain Metastasis Clinic at the University of Texas MD Anderson Cancer Center. Her case was reviewed by a neuroradiologist, a neurosurgeon, a radiation oncologist, and a medical oncologist. Because of the resolution of her initial neurologic symptoms and the atypical presentation of a large brain metastasis without any mass effect or edema, the multidisciplinary recommendation was to forgo surgery and continue systemic therapy with plans to repeat a brain MRI in 4–6 weeks. The patient was started on treatment with liposomal doxorubicin for systemic and not intracranial disease progression. A follow-up

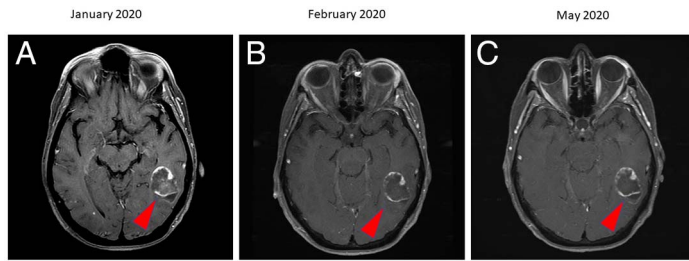


Figure 1. (A) The T1 post-contrast magnetic resonance image of the brain in a 42-year-old woman with metastatic hormone-positive breast cancer in January 2020 showed a 3.8×2.9 -cm well-demarcated lesion involving the posterior medial and inferior temporal gyri with a 1.1×0.9 -cm enhancing nodule. (B) Repeat imaging in February 2020 showed a minimal decrease in lesion size, which then measured 3.7×2.8 cm. (C) Additional imaging performed in May 2020 showed the 3.7-cm previous cystic left temporal lesion unchanged, but with the development of eight new supratentorial metastases measuring up to 4 mm.

brain MRI performed in February 2020 showed no change in the size of the large cerebral lesion, and she continued chemotherapy (Fig. 1B). In May 2020, a brain MRI demonstrated eight new supratentorial lesions measuring up to 4 mm; however, the previous 3-cm metastasis remained unchanged (Fig. 1C). Because of new brain metastases, WBRT was recommended.

DISCUSSION

Breast cancer is the second most common cancer type causing brain metastases after lung cancer.^[6] Several factors in breast cancer are associated with developing brain metastasis, including young age, high tumor burden, high nuclear grade, triple-negative disease, HER2 overexpressing tumors, and positive nodal disease.^[7] Evaluation for central nervous system metastases by brain MRI is not routinely performed. Current guidelines do not recommend routine MRIs for patients with breast cancer, even at high risk, unless symptoms are present.

During replication, DNA is exposed to exogenous and endogenous factors that can generate single-strand (SS) or double-strand (DS) DNA breaks. The PARP protein initiates the repair process of SS breaks.^[8] Without the PARP complex, SS breaks progress to DS breaks, requiring a more sophisticated repair process called the homologous repair (HR) pathway. Loss or inactivation of both copies of HR genes such as *BRCA1*, *BRCA2*, *ATM*, *ATR*, *CHEK1*, *CHEK2*, *RAD50*, *RAD51*, *RAD51C*, and *RAD54L* generate DNA repair errors and cause cell death.^[9] As a consequence, *BRCA1/2* were rapidly adopted in clinical practice given the predictive biomarker value with a significant correlation with the clinical response to PARPi. In addition, since the clinical development of tumor sequencing in clinical practice, molecular testing for other HR genes, including *ATM*, *ATR*, *CHEK1*, *CHEK2*, *RAD50*, *RAD51*, *RAD51C*, and *RAD54L*, gained traction over the past years.

Genetic testing for *BRCA1/2* mutations has been adopted into clinical practice, and in addition to familial implications, these represent predictive biomarkers for PARPi.^[9,10] Mutations in the *ATM* gene are associated with an elevated risk of breast cancer (up to two- to fourfold above the general population) and possibly other cancers.^[10] Genetic testing for ATMs has gained attention recently. However, there are data suggesting that not all patients with ATMs have functional loss of ataxia-telangiectasia.^[11]

Based on the findings of a phase III, open-label, randomized trial in patients with germline *BRCA1/2*-associated metastatic breast cancer, talozaparib gained Food and Drug Administration (FDA) approval.^[12] Although initial preclinical results have shown limited blood-brain barrier (BBB) penetrance of PARPi, several preclinical models with a disrupted BBB secondary to central nervous system malignancy have shown efficacy in brain lesions to PARPi.^[13] Furthermore, a few recently published case reports have demonstrated encouraging efficacy with maintenance PARP inhibition in patients with germline *BRCA1/2* mutations and brain metastases.^[14–16]

Currently, multiple clinical trials are exploring the effect of PARPi and other DNA damage repair targeting agents in patients with ATM mutations.^[17–19] ATM has been potentially matched with PARPi, like in the clinical trial in which the patient was enrolled.^[13,14] Emerging results show that ATMs are better predictive biomarkers for treatment with ATR inhibitors preferentially as compared with PARPi.^[15] This is mainly because there is some evidence that PARPi might have cytostatic and not cytotoxic effect in case of ATMs.^[11]

However, the role of these drugs in the context of brain metastases remains unknown, mainly because early phase I clinical trials often exclude patients with brain metastases. The FDA and the American Society of Clinical Oncology have recommended enrolling patients with brain metastases in clinical trials and developing specific clinical trials to evaluate the role of targeted therapies within this subset of patients.^[16]

Our patient was treated with multiple lines of systemic therapy, including chemotherapy and hormonal therapy. Because of an ataxia-telangiectasia germline mutation, a genomically matched treatment with PARPi on a clinical trial was initiated. Because of the resolution of her neurologic symptoms after the start of PARPi, we can hypothesize that the large brain metastasis might have developed before the treatment with the PARPi, and the growth of the brain metastasis was halted while on this therapy. This would explain the brain MRI findings in January 2020 consistent with a “treated” lesion, although the patient did not receive any prior radiation to the brain.

Considering our hypothesis of the brain metastases predating PARPi therapy, the patient had clinical benefit of the brain lesion with a duration of response over 10 months (April 2019–January 2020). Nevertheless, after

careful radiologic reevaluation of previous PET-CTs over the past year, in retrospect, a lesion could be suspected in the same area (Supplemental Fig. 2). However, the role of 18F-FDG PET-CT in detecting unsuspected brain metastases remains low because of physiologically high background FDG uptake. This supports prior research that PARP inhibition may be effective by crossing the BBB, as reported in other publications.^[17]

Usually, patients with large brain metastases who are symptomatic or could become symptomatic are considered for surgical resection followed by radiation of the resection cavity. Patients with fewer than 10 lesions are treated with stereotactic radiosurgery, whereas patients with more than 10 lesions are often treated with whole-brain radiation.^[3] However, these recommendations should be personalized for each patient. The multidisciplinary approach is vital in evaluating the radiologic aspect of the lesion, the patient's symptoms, the overall tumor burden, and systemic treatment options.^[18]

For our patient, because of the absence of neurologic symptoms and concern over the size and number of lung metastases, starting a new line of systemic treatment was recommended, and a repeat brain MRI was planned for 4–6 weeks later. The large brain metastasis remained stable in the subsequent radiologic examinations for more than 4 months when she presented new brain metastases, raising the question if the large lesion was the source of intracranial seeding. The multidisciplinary brain metastases team recommendations avoided possible complications and morbidity related to craniotomy and delayed radiation.

CONCLUSION

In summary, this case report exemplifies the importance of the multidisciplinary management of patients with brain metastases. It suggests that treatment for large brain metastasis should consider more than the tumor size. Optimal treatment planning should instead be individualized following a multidisciplinary case review. Furthermore, this highlights the value of genomically matched targeted therapy based on tumor molecular profiling. The safety and efficacy of systemic targeted treatments for patients with germline ATMs with breast cancer and brain metastases remain to be further evaluated in clinical trials.

Supplemental Material

Supplemental materials are available online with the article.

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