The BRCA-1 and BRCA-2 suppressor genes are involved in DNA repair via homologous recombination resulting in genomic instability and loss of function mutations confer a predisposition to malignant transformation. BRCA genes and gene products interact with a number of regulator proteins involved in a multitude of pivotal cellular processes such as maintenance of chromosomal stability, cell cycle control, and apoptosis. Their discovery led to the first real-world application of synthetic lethality expediting the drug development of PARP inhibitor and personalized medicine in patients bearing such mutations.

BRCA-1 associated phenotype is characterized by an increased risk for female and male breast cancers, ovarian cancer including the fallopian tubes, and primary peritoneal cancers. The phenotype spectrum of BRCA-2 associated malignancies is much broader than that of BRCA-1 and includes solid cancers such as breast, ovarian, prostate, gall bladder, gastric, pancreatic cancer and melanoma, and hematologic malignancies such as acute, and chronic myeloid leukemia, acute promyelocytic leukemia, chronic lymphocytic leukemia, non-Hodgkin lymphoma and Fanconi anemia.

The BRCA-2 phenotype continues to evolve into a seemingly delayed fuller spectrum that includes other entities such as CNS malignancies. Initial evidence of a possible genetic link came with metachronous clinical observations between the development of breast cancer and various other neurologic neoplasms. Several authors have reported that meningioma occur more frequently in patients with a history of breast cancer. Piccirilli et al. recently described the occurrence of glioblastoma multiforme (GBM) in eleven Italian patients previously treated for breast cancer, although no mutational analyses were performed. As BRCA-2 pathways are better understood, several component BRCA-2 gene proteins, and their protein-protein interactions are now emerging as having important roles in neural regulation and development, with evidence suggesting that defects in this pathway contribute to the formation of primary neurologic malignancies, including GBM.

We present this case study which represents an extended natural historical account of a BRCA-2 phenotype. It is an in-depth, multifaceted exploration of the complex issues in the real-life setting of a BRCA-2 deleterious mutation. It also suggests adding at least two other features to the BRCA-2 phenotypic picture, that is, a potential curative chemosensitivity in low-burden metastatic settings and increased potential for delayed CNS malignancies. These new phenotypic features in turn may advance clinical options for these inherited disorders such as adjuvant and secondary prevention use of PARP inhibition.

**CASE REPORT**

The patient is a 57-year-old Caucasian female, who at the age of 24 was noted to have JAK2 positive myeloproliferative disorder in the form of essential thrombocytosis with a platelet count over 1.5 million, requiring hydroxyurea. She presented at age 31 with a 5 cm mass in the left breast, which was a moderately differentiated infiltrating ductal carcinoma with two involved lymph nodes, and hormone receptor positivity. The patient underwent six cycles of fluorouracil, doxorubicin, and cyclophosphamide (FAC) chemotherapy. At age 33, she developed metastatic disease with involvement of the left superior acetabulum, with cortical destruction. She was treated with radiation therapy and hormone therapy. At age 34, she underwent triple alkylation chemotherapy with autologous stem cell rescue. The conditioning regimen consisted of high dose carboplatin (600mg/m2), thiotopea (900mg/m2), and cyclophosphamide (180mg/kg). Since high dose chemotherapy, she has remained in remission with no evidence of disease on tomographic and nuclear medicine imaging. Genetic testing in November of 2015 detected a deleterious BRCA-2 mutation with a 5104delAA. Her mother and sister were also positive for the same BRCA-2 mutation. She underwent an elective risk-reducing laparoscopic hysterectomy, with bilateral salpingo-oophorectomy and was found to have a superficially invasive 1 cm endometrioid adenocarcinoma involving less than 50% myometrium. She received no adjuvant therapy.

In January of 2017, she developed weakness in her right arm, headaches, and confusion with expressive aphasia. Magnetic Resonance Imaging (MRI) of her brain showed a large complex cystic mass measuring 4.2 x 2.7 cm in the left frontal region, with surrounding vasogenic edema. There was a noted area in the scan of abnormal signal intensity in the contralateral periventricular white matter suspicious for multicentric disease. The patient underwent a left parietal craniotomy for a gross total resection of the mass in the left frontal lobe. Pathology was consistent with GBM, WHO grade 4, IDH-1 wild type, by immunohistochemistry. The tissue was negative for P53, MGMT promoter methylation, and EGFR mutation was not detected. Postoperative MRI showed left parietal craniotomy with postsurgical changes in the high left frontal lobe.

There was interval decrease in the size of the previously demon-
stratified left frontal lobe lesion; however, peripheral nodular enhancement continued, presumably representing residual disease/local recurrence. Also noted was a new enhancing bilobar lesion in the right frontal lobe measuring 1.4 x 1.3 x 2.6 cm, and new enhancing lesion in the left thalamus measuring 0.4 cm. She received external beam radiation therapy concomitantly with temozolomide at 75 mg/m² during the course of radiation therapy. Radiation therapy covered the site of resection and thalamic lesion. She continues monthly pulses of temozolomide with concurrent low-intensity electric tumor-treating field therapy with the Optune device.

**DISCUSSION**

Over the last 20 years, there has been considerable progress in our understanding of cancer susceptibility genes. Previous retrospective clinical studies had grouped both BRCA-1 and 2 mutations to assess potential associations with cancer outcomes, often with conflicting results. Most of those studies were statistically underpowered to differentiate the effects of BRCA-1 and BRCA-2 in terms of chemosensitivity, treatment outcomes, prognosis, and survival.

This case study serves to emphasize unique characteristics of BRCA-2 pathology. It serves to highlight research into the effect of the presence of BRCA-2 mutations on (a) chemosensitivity and treatment outcome, (b) the possibility of GBM being part of BRCA-2 phenotype, (c) germline BRCA-2 mutation predisposing to a JAK2-related clonal hematopoiesis and myeloproliferative neoplasms and finally, (d) potential advantage of using PARP inhibitors concomitantly with temozolomide to counter drug resistance in the treatment of the GBM, as well as potential justification for adjuvant and secondary prevention in patients with BRCA-2-associated malignancies.

Preclinical studies conducted in both mice and human cell lines without functional BRCA-1 and 2 proteins have an increased sensitivity to chemotherapeutic agents that cause double-strand breaks, such as platinum and anthracyclines. However, clinical trials assessing outcomes in BRCA-1 and BRCA-2-related malignancies compared to sporadic breast cancer patients have yielded conflicting results. Most of those clinical studies have been retrospective and biased, as initial outcome reports come from genetic screening centers. Robson et al were the first to report differential clinical outcomes between BRCA-1 and BRCA-2 in the adjuvant setting. They reported on retrospective adjuvant therapy studies that demonstrated differential clinical outcomes among Ashkenazi women with either BRCA-1 or BRCA-2 breast cancer receiving adjuvant chemotherapy for early stage invasive breast cancer. At a median follow-up of 116 months, breast cancer-specific survival was worse in women with BRCA-1 mutations (62% vs 86%, P<0.0001) than in those without the mutation. Women with the BRCA-2 mutation had significantly better outcomes of specific survival (84% vs 86% P=0.76).

This chemosensitivity BRCA-2 trait has also been demonstrated in the metastatic setting. Krieger et al, studied 93 BRCA-1 and 28 BRCA-2 associated metastatic breast cancer patients treated with anthracycline-based regimen cyclophosphamide/methotrexate/fluorouracil (CMF therapy). As compared to sporadic cases without the BRCA gene mutation, BRCA-2-associated patients had a significantly higher overall survival (89% vs 50% non BRCA cancers; P=0.001). They also had longer progression-free survival with a hazard ratio of 0.64; P=0.04, and prolonged overall survival with a hazard ratio of 0.53; P=0.005 after start of first line chemotherapy for metastatic breast cancer. For BRCA-1 related cancers, no statistically significant higher chemosensitivity was observed.

Remarkably, in a case study similar to the one presented here, Huang et al reported a patient who developed bone involvement despite adjuvant hormonal therapy for early stage breast cancer, who was treated with tandem autologous bone marrow transplantation, and high dose alkylator- and platinum-based conditioning regimens. A complete clinical and radiological remission has been maintained for 11 years. In an attempt to investigate this unusual and sustained complete remission, BRCA-1 and BRCA-2 mutational analysis was performed. A BRCA-2 8765del AG was identified. Our case study patient appears to be the second reported BRCA-2 case of sustained remission of 23 years.

This case study further expands phenotypic definition of the natural history of BRCA-2 associated metastrophic CNS malignancies. Both BRCA-1 and 2 gene proteins and their protein-protein interactions are now emerging as having important roles in neural regulation and development. Indeed, BRCA-2 is essential for normal neurogenesis. Studies with murine models have shown that neurogenesis is a DNA damage-induced apoptosis phenomenon, where by the tumor suppressor gene P53 deficiency abrogates the developmental defects caused by BRCA-2 loss, but leads to formation of medulloblastomas. There is mounting clinical biochemical and genetic evidence that proteins involved in homologous recombination repair through the BRCA-1 and BRCA-2 pathways are important in the development of brain malignancies, particularly medulloblastomas and astrocytomas.

The patient reported here presented with a multicentric GBM. Multicentric GBMs are considered rare, comprising only 2 - 9% of all GBMs. Multicentric gliomas are well-separated lesions, located in different lobes or hemispheres and cannot be ascribed to dissemination through commissural pathways, cerebrospinal fluid, blood or local extension. Furthermore, multicentric GBM associated with other primary cancers is extremely rare. This appears to be the first case of multicentric GBM associated with BRCA-2. A similar multicentric GBM was reported by Elmariah et al in a patient with BRCA-1 invasive breast cancer, and may be included as part of the BRCA clinical phenotype. This clinical feature may also affect clinical management of such patients with BRCA deleterious mutations presenting with multifocal brain lesions, and may need diagnostic histology confirmation of more than one lesion for accurate histologic diagnosis and tumor debulking.

This case report also describes the initial presentation of a myeloproliferative disorder seven years prior to development of breast cancer, ten years prior to developing uterine cancer, and fourteen years prior to development of GBM. Using genome wide association studies (GWAS) to identify novel predisposition alleles associated with myeloproliferative neoplasm and JAK2 V617F clonal hematopoiesis in the general population, Hinds et al showed germline variants CHEK2, ATM, PINT, and GFI1B endowed individuals with a predisposition to JAK2 V617F clonal hematopoiesis. Our case study may be the first reported case of a somatic JAK2 mutation myeloproliferative disorder associated with a germline BRCA-2 breast cancer patient, and can be added to the evolving phenotype of BRCA-1 and
2 germline disorder, or perhaps, even the concept of “BRCA-ness” traits in sporadic malignancies.

Even with aggressive surgical resection, using state of the art technology, preoperative and intraoperative neuroimaging, along with recent advances in radiotherapy and chemotherapy, the prognosis for GBM patients remains dismal. One of the reasons for treatment failure is the patient’s acquired resistance to chemotherapeutic agents. Temozolomide is the current first-line chemotherapy agent for GBMs with adequate blood-brain barrier penetration and limited bone marrow toxicity. Its mechanism of action involves the addition of methyl groups to several DNA strand breaks and eventually growth arrest and apoptosis; however, virtually all GBMs develop secondary treatment resistance after administration of either temozolomide, radiation, or a combination of temozolomide and radiation.28 Poly (adenosine-diphosphate ribose) polymerase (PARP) inhibitors are novel biologic agents that have become important in BRCA-1 or BRCA-2 mutated malignancies, and PARP inhibition will likely play a major role in the management of BRCA associated neurologic malignancies.29 With the recent observations that olaparib crosses the blood-brain barrier, and in-vitro evidence shows that the addition of olaparib to temozolomide restores apoptotic sensitivity, it is now entering Phase II/III clinical trials in combination with temozolomide in the treatment of GBMs.

Since its discovery by Michael Stratton and co-workers 22 years ago,30 BRCA-2 has been one of the most thoroughly investigated human cancer genes. Its discovery has spawned new directions in molecular understanding, cancer-drug development, and genetic counseling strategies, which all help save countless lives through hypothesis-based associations. Its full phenotypic spectrum and genetics continue to exponentially evolve to hypothesis-free genomewide association studies (GWAS) as we move forward with near-population based testing to identify genetic modifiers of cancers risk in BRCA-1 and BRCA-2.31 Meanwhile, the potentially curative chemosensitivity that this BRCA-2 patient demonstrated may justify the potential adjuvant or secondary prevention use of PARP inhibition in similar patients. It is hoped that this case study, and other similar reports, will promote better understanding of the unique clinical and molecular aspects of BRCA-2 pathology.

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