CNS Metastasis and Ovarian Carcinoma. Is *BRCA* Mutation an Ally? - A Case Report

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Abstract

Despite advances in medical diagnostics and treatment, ovarian carcinoma continues to be a disease detected at a late stage when metastasis has occurred. Ovarian cancer spreads early to the peritoneum resulting in massive and rapidly accumulating ascites. Central nervous system metastasis, though rare has been reported. Here, we report a case of papillary serous carcinoma of the ovary in a sixty-year-old female who had florid metastasis involving the brain and the spinal nerve roots. Her cancer was detected when intra-abdominal spread had occurred; however, she did achieve a period of clinical remission with chemotherapy and PARP inhibitors. Her treatment included neo-adjuvant chemotherapy with carboplatin and paclitaxel, debulking of the tumor, and adjuvant chemotherapy with carboplatin and docetaxel. When her disease relapsed, she was started on a PARP inhibitor Niraparib which kept her in remission for another year. Her genetic testing was positive for the BRCA 1 mutation. She developed metastases to the brain and spinal cord with involvement of the spinal nerve roots. She ultimately developed carcinomatous meningitis and succumbed to the disease. It was of interest to speculate the reason for this pattern and degree of spread of her cancer. Do genetic mutations have a role to play? Data is sparse on the role of BRCA mutations as being a contributor to early or aggressive spread in ovarian cancer.

Keywords: CNS Metastasis; Ovarian cancer; BRCA Mutation; Intramedullary metastasis; Spinal root metastasis; Carcinomatous meningitis

Introduction

According to the American Cancer Society, ovarian cancer is one of the top five leading causes of cancer-related death in women. The treatment for ovarian cancer is advancing and has enabled women with ovarian cancer to live longer. However, with a longer life span, patients are now being diagnosed with metastatic lesions at locations that were previously considered rare. Central nervous system (CNS) involvement in patients with ovarian carcinoma varies between 0.29 and 11.6%, commonly involving the cerebrum, cerebellum, pons, and the meninges [1]. Metastasis to the nerve roots is rare and has been described infrequently in the literature. We outline a case of carcinomatous meningitis with involvement of the spinal nerve roots and rapid progression of the disease despite a period of remission with a PARP (poly ADP ribose polymerase) inhibitor. This discussion also aims at exploring the relationship of *BRCA 1/BRCA 2* (BReast CAncer gene) mutational statuses and aggressive metastatic disease.

Case Presentation

A 60-year-old woman with a past medical history of hypothyroidism, hypertension, DCIS (ductal carcinoma *in-situ*), presented to the hospital with increasing abdominal girth, constipation, fatigue and anorexia present since a few weeks. She was an active smoker, with a 30 pack-year smoking history. Family history was unknown as she was adopted. She had three daughters of her own. On presentation, she appeared healthy except for a markedly distended abdomen. A papable periumbilical mass was present on palpation and there was evidence of fluid wave. All of her laboratory values were within normal limits, except for an elevated cancer antigen 125 (CA 125) level to 6546 U/ml.

A computed tomography (CT) scan of the abdomen was performed, which demonstrated massive ascites and obvious peritoneal carcinomatosis. A left-sided ovarian cyst was seen, which was consistent with a cystic ovarian tumor. There was also nodularity and induration along the greater omentum, and scattered retroperitoneal nodes. An ascitic fluid tap revealed atypical cells, concerning for adenocarcinoma. She underwent a percutaneous biopsy of the pelvic mass, and the pathology revealed papillary serous carcinoma of the ovary with extensive psammoma bodies.

She was diagnosed with stage IV ovarian adenocarcinoma with peritoneal and retroperitoneal metastases. She underwent 6 cycles of neo-adjuvant chemotherapy with carboplatin at AUC of 6 and paclitaxel 175 mg/m^2 every 3 weeks. She then underwent debulking surgery with minimal residual disease. She received two cycles of adjuvant chemotherapy with carboplatin and docetaxel. Meanwhile, her genetic testing came back positive for the deleterious *BRCA 1* mutation. Two of her three daughters were also found to be carriers. She was followed periodically for surveillance monitoring. She had achieved clinical remission for more than a year when her CA 125 levels started to rise again. At that time, Niraparib (PARP inhibitor) 300mg was started. About 1.5 years later, her CA 125 levels began rising again. Over the next four months, she rapidly deteriorated with morning headaches, ataxia, and memory disturbances and was struggling at work with these impairments. She also had periods of staring episodes, suggestive of absence seizures. MRI brain was then done, which showed a single large right parietal metastasis. She underwent resection of the metastasis (Figure 1 for histopathology and Figures 2a & 2b for immunohistochemistry staining of resected specimen), followed by whole-brain radiation.

A few weeks later, she presented to the hospital with complaints of sudden onset of numbness to lower extremities and upper extremities for a week. She also sustained mechanical falls secondary to numbness. MRI of the brain showed no acute intracranial process but only postsurgical changes. MRI of the total spine showed enhancing lesions within the nerve roots of the cauda equina measuring 7 mm (Figure 3) as well as enhancement in the right foramen at T1 (Figure 4). She received steroids and total spine radiation for spinal and nerve root metastasis. She was slowly improving but acutely deteriorated soon after with urinary incontinence and increased weakness and confusion. She

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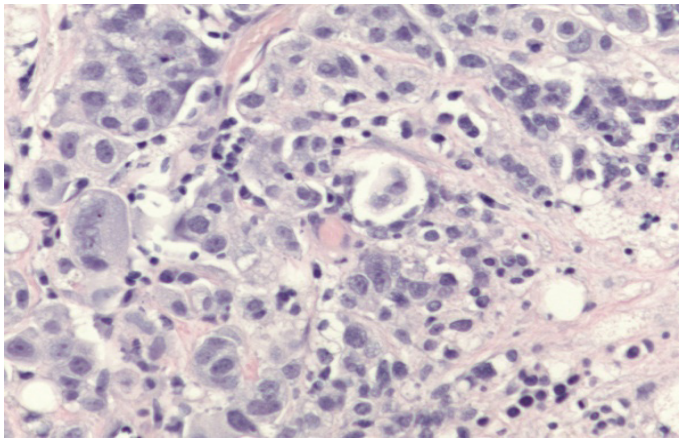
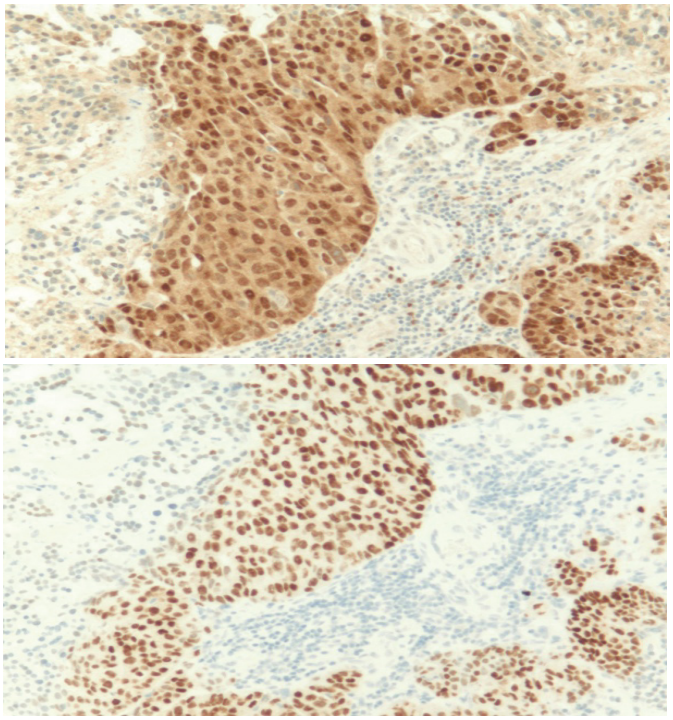


Figure 1. Histopathology of resected brain metastasis specimen. H&E stain.20x magnifications respectively showing a high grade adenocarcinoma with necrosis.



Figures 2a & 2b: Immunohistochemistry stain on resected brain metastasis specimen. The stain for PAX8 and Wilms tumor (which are the two brown stains), are positive and the combination of the two are consistent with a high grade ovarian primary serous carcinoma. PAX8 is positive in GYN tumor. The Wilms tumor is positive in serous carcinomas of GYN origin and also in mesothelial cells. The combination of the two favors GYN origin of a serous carcinoma.

was admitted for carcinomatous meningitis with MRI of the brain showing progression of the disease. CSF studies showed glucose <10mg/dl, protein 639mg/dl, and cell cytology positive for malignant cells consistent with high-grade serous ovarian carcinoma. Given the advanced stage of her disease, she was transitioned to home hospice but unfortunately passed away during the hospitalization.

Discussion

Ovarian cancer represents one of the most common gynecological malignancies and has the highest mortality of all female reproductive cancers [2]. Ovarian cancers are aggressive, difficult to treat and are associated with late-stage diagnosis due to lack of early symptoms. Early intra-abdominal metastasis is common. They metastasize to other sites, with a rare predilection

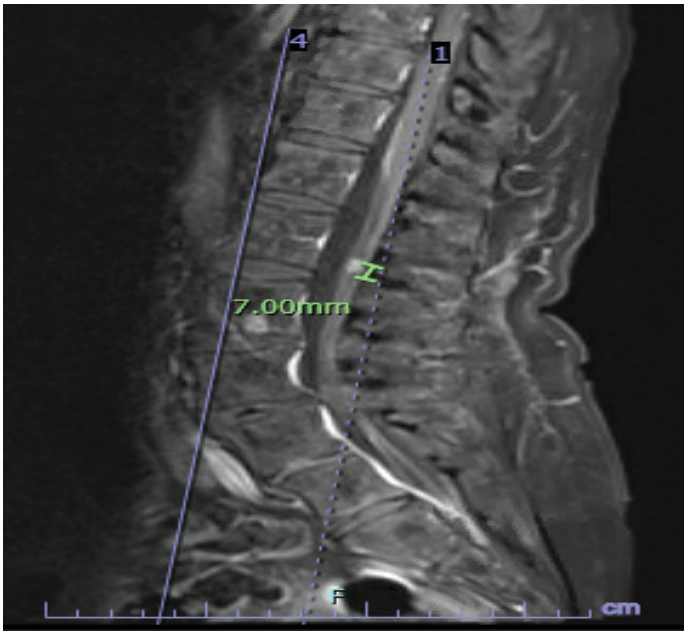


Figure 3. MRI of thoraco-lumbar spine. Mid sagittal view. Enhancing lesion within the nerve roots of the cauda equina measuring 7 mm. Metastatic deposit cannot be ruled out.

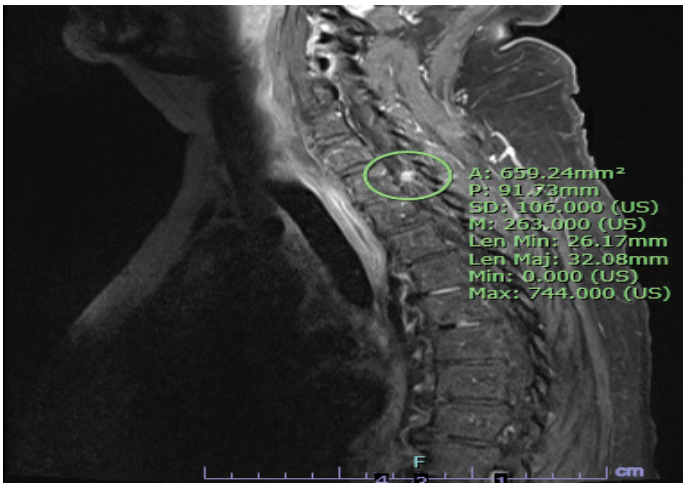


Figure 4. MRI of thoracic spine. Mid sagittal view. Focus of enhancement in the right foramen at T1. The possibility of additional mass cannot be ruled out

to the CNS. Carcinoma of the lung has the most propensities for intramedullary metastases, followed by breast carcinoma, melanoma, renal cell carcinoma, colorectal tumors, cervical carcinoma and lymphoma [3]. Intramedullary metastases is uncommon, with only a few cases of spinal root metastasis reported so far, all of which have carried a grave prognosis [4]. The prevalence of CNS metastasis in ovarian carcinomas is increasing due to prolonged life span after chemotherapy induced remission as well as poor permeability of chemotherapy through the blood brain barrier [5]. In a systematic review by Pakneshan et al., [6] 591 patients were found to have ovarian cancer metastatic to the central nervous system, however only 1% were noted to have metastasis to the spinal cord. Cerebellum was noted to be the most common site of intracranial metastasis for ovarian cancer [6].

Sekine et al. analyzed 347 with ovarian cancer. Seven were noted to have metastasis to the brain. One of these cases had clear cell adenocarcinoma, while the six others had serous adenocarcinoma.. Of these 7 cases, 4 patients had a family history of ovarian and/or breast cancer. All the patients had received taxane-platinum based regimens either as adjuvant or neoadjuvant chemotherapy before the diagnosis of the brain metastases. Their results suggested that

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the loss of *BRCA1* function may be implicated in ovarian cancer metastasis to the brain [7].

What factors contribute to early aggressive disease? Do *BRCA 1*/2 mutations have more propensities for CNS metastasis? A study at Dana Farber Institute specifically looked into whether germline *BRCA 1*/*BRCA* 2 mutation status in patients with breast cancer is independently associated with CNS involvement. CNS involvement was more frequent in women with germline *BRCA1*/*BRCA2* mutations who had metastatic breast cancer. *BRCA2* carriers had a higher frequency of CNS metastasis than non-carriers when controlled for breast cancer subtype [8]. In another study trying to estimate the frequency of HBOC in women with CNS metastasis from epithelial ovarian cancer (EOC), out of 1240, 32 cases of EOC with CNS metastasis were identified (2.58%). Among those with personal and family history, 66.7% (20/30) were suspicious of HBOC syndrome. Among those who underwent germline testing, 71.43% (5/7) had a pathogenic *BRCA* mutation [9].

Genetic studies and analysis are important as they throw light on potential treatment options such as small molecule targeted therapies. In one study, Next-Generation Sequencing was used to evaluate the mutational profile of 8 cases of ovarian cancer with. All 8 sequenced brain metastasis (BM) samples exhibited alterations. The most commonly mutated genes were *BRCA1*/2, TP53, and ATM. In total, 7 out of the 8 samples revealed either a *BRCA1* or a *BRCA2* pathogenic mutation, and all 8 BM samples showed mutations in at least one DNA repair gene. These findings strongly imply that the mutations of *BRCA* and DNA repair genes are significant in ovarian cancer metastasizing to the brain. Based on these findings, pharmacological PARP inhibition is thought to be a potential targeted therapy in ovarian cancer with brain metastasis [10]. Lack of spinal cord symptoms does not exclude intramedullary spinal cord metastasis. Treatment modalities involve surgical resection of accessible sites, chemotherapy as well as radiotherapy [11]. Steroids can be helpful as it can provide symptomatic relief by reducing the edema around the tumor [10].

In the systematic review by Pakneshan et al., factors that were associated with better survival were young age, and high Karnowsky performance scale score. The prognosis was not affected by the grade or stage of the tumor, pathology of the ovarian tumor, CA 125 levels, or the presence of extra cranial metastasis. The number of brain lesions, however, contributed to the survival with longer survival in patients with a single lesion (21.4 months), when compared to multiple lesions (9.2 months) [6-11]. Ultimately, the management of metastatic disease depends on the extent of the disease, the patient's functional status, and their palliative goals.

Conclusion

Spinal cord metastasis of ovarian cancer is associated with high mortality. It is estimated that about 80% succumb within three months of diagnosis. The guidelines for the treatment of patients with such metastasis are not well established. Hence a multi-disciplinary approach must be utilized early in the course of the disease to formulate an individualized treatment plan. Is there a role for prophylactic radiotherapy? Further studies are needed to answer these questions to adequately manage and prevent these deadly complications.

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Ethics approval

Not Applicable.

Statement of Compliance

Not Applicable.

Clinical Trial Transparency

Not Applicable.

Author Contributions

Radhika Kulkarni and Meghana Singh for preparation of the manuscript. James Vredenburgh for expert opinion and proof reading.'

Competing Interests

All authors have no competing interests to declare.

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