Gynecologic Oncology Reports 51 (2024) 101322

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Successful treatment of stage IVB ovarian carcinosarcoma with PARP Inhibitor: A case report

Jessica D. St. Laurent [a], Mary Kathryn Abel [a], Joyce Liu [b], Bradley J. Quade [c], Michelle R. Davis [a,*]

[a] Division of Gynecologic Oncology, Department of Obstetrics, Gynecology and Reproductive Biology, Dana-Farber Cancer Institute, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA
[b] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston MA, USA
[c] Division of Women's and Perinatal Pathology, Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Keywords:
Carcinosarcoma
STIC
Ovarian carcinoma

1. Introduction

Ovarian carcinosarcoma (OCS) is a rare, biphasic tumor of the fallopian tube, ovary, and peritoneum that accounts for less than 5 % of all ovarian carcinomas. At the time of diagnosis, more than 90 % of OCS will have spread beyond the ovary (Berton-Rigaud et al., 2014). Compared to the most common histotype high grade serous ovarian carcinoma (HGSOC), OCS is associated with a lower median overall survival reported at 16 months (Mano et al., 2007). The understanding and management of OCS remain challenging due to its rarity and limited treatment options. Current therapeutic strategies primarily involve surgical intervention followed by chemotherapy similar to standard management for HGSOC (See et al., 2019). However, due to the aggressive nature of OCS and its propensity for metastasis, novel treatment approaches are urgently needed.

Recent studies including case reports and small case series have described the potential association between OCS and germline mutations, particularly those involving the *BRCA* gene (Ripamonti et al., 2018). The presence of *BRCA* mutations in patients with OCS suggests a possible role in the development and progression of this malignancy. PARP inhibitors (PARPi) have emerged as a promising class of drugs for the treatment of ovarian cancers, especially in patients with *BRCA* mutations. PARPi exploit the concept of synthetic lethality, wherein cancer cells with defective DNA repair pathways, such as those harboring *BRCA* mutations, become highly susceptible to PARP inhibition. The success of PARPi in other ovarian cancer subtypes has prompted investigation into their efficacy in OCS, particularly in the context of *BRCA* mutations (Pennington et al., 2014).

This case report describes the unusual presentation of a patient with a known germline *BRCA1* mutation, found to have metastatic carcinosarcoma in the left inguinal node who ultimately underwent successful treatment using a PARP inhibitor. The presented case contributes to the growing body of evidence supporting the potential role of PARPi as a therapeutic option for OCS patients, particularly those with *BRCA* mutations.

2. Case summary

A 36-year-old G2P2 female with a known germline *BRCA1* mutation presented with a new non-tender palpable mass in her left inguinal region. She had previously declined risk reducing surgery and had been followed with serial CA-125 s and pelvic ultrasound for surveillance. Her medical and surgical history were notable for a diagnosis of ductal carcinoma of the left breast in 2010, which was treated with neoadjuvant chemotherapy and bilateral mastectomy followed by three years of tamoxifen. Additionally, the patient had a prior loop electrosurgical excision procedure (LEEP) for cervical dysplasia and a body mass index of 27. Her family history was notable for three first degree maternal relatives with breast cancer including her sister (diagnosed at age 26) and one sister with ovarian cancer (age 34).

* Corresponding author at: Division of Gynecologic Oncology, Brigham and Women's Hospital, 75 Francis St. ASB1 3rd Floor, Boston, MA 02115, USA.
E-mail address: mdavis31@bwh.harvard.edu (M.R. Davis).

https://doi.org/10.1016/j.gore.2024.101322
Received 15 November 2023; Received in revised form 31 December 2023; Accepted 2 January 2024
Available online 3 January 2024

Physical exam by her provider demonstrated a new palpable, fixed 2 cm mass in the left groin. A PET-CT revealed a 2.4 cm FDG avid left inguinal lymph node and mild FDG avidity in the endometrial canal (Fig. 1A and B). She underwent an endometrial biopsy that showed benign endometrium and a left inguinal biopsy demonstrating high grade adenocarcinoma with a biphasic component consistent with a Mullerian origin. Her CA-125 was 170 U/mL from 36 U/mL on prior evaluation. The patient was referred to a gynecologic oncologist and was counseled to undergo surgical debulking surgery based on pathologic results and imaging findings suggesting isolated metastatic disease to the left inguinal region.

She was taken to the operating room for a left inguinal lymph node dissection and laparoscopic intra-abdominal staging procedure. Laparoscopic evaluation was notable for a grossly normal upper abdomen with no disease visible along peritoneal surfaces and a normal appearing omentum. The pelvis contained endometriosis, confirmed by histopathology, as well as adhesions along the posterior cul de sac and the uterine serosa. The fallopian tubes and ovaries were bilaterally enlarged with an obviously thickened and edematous region of the right fallopian tube without surface excrescences. No pelvic or paraaortic lymphadenopathy was appreciated and given prior negative PET-CT and known inguinal involvement, additional staging lymphadenopathy was deferred. The patient underwent an uncomplicated total laparoscopic hysterectomy, bilateral salpingo-oophorectomy with resection of pelvic peritoneum, removal of a nodule from the sigmoid mesentery, and omentectomy. Following the intra-abdominal portion of the procedure, the left inguinal region was assessed via an incision parallel to the inguinal ligament and was notable for a 2 cm firm, encapsulated mass that was removed intact along with surrounding nodal tissue. At the end of the procedure, all visible disease was removed, and the patient had an unremarkable post-operative recovery.

Pathologic analysis was diagnostic for metastatic Mullerian carcinosarcoma involving the left inguinal lymph node (Fig. 2A) and a serous tubal intraepithelial carcinoma (STIC) arising in the left fallopian tube (Fig. 2B). Immunohistochemistry of the STIC showed overexpression of p53, consistent with mutation, as well as WT-1 and elevated Ki-67 expression, supporting the histological diagnosis of STIC. The epithelial component of the carcinosarcoma had a Solid, Endometrioid or Transitional (SET)-like morphology associated with serous carcinoma of the adnexa. The mesenchymal component had both spindle cell and focal heterologous chondrosarcomatous differentiation with the intraepithelial neoplasia present in the left fallopian tube regarded as the site of origin.

This patient was classified as having stage IVB ovarian carcinosarcoma based on involvement of her inguinal lymph node. She received 6 cycles of carboplatin and paclitaxel chemotherapy that she completed four months after her initial surgery. Given her germline *BRCA1* mutation, she started Olaparib maintenance therapy. After 4 months on maintenance therapy, she endorsed extreme fatigue and nausea unrelieved by anti-emetics and was dose reduced to 250 mg twice daily which she continued for the duration of her treatment without issues. She was followed with monthly surveillance laboratory studies including CA-125 and imaging surveillance with CT scans of the chest abdomen and pelvis every 3–6 months while on maintenance therapy. Her last imaging was at the completion of maintenance therapy without evidence of disease. At her last follow-up three years and six months after her initial diagnosis, her CA-125 was 4 U/mL and she was without evidence of disease on physical exam.

3. Discussion

This case report presents a compelling example of successful treatment for a patient with *BRCA*-associated ovarian carcinosarcoma using a PARP inhibitor. While the presentation was unusual, with a STIC only identified in the left fallopian tube and metastatic carcinosarcoma in the inguinal node and no other local or distant site of invasive carcinoma, the favorable response observed in this patient provides support for the potential benefits of PARP inhibitors in the management of BRCA-mutated ovarian carcinosarcoma.

STIC lesions are believed to be precursor lesions to *BRCA*-mutated high-grade serous carcinoma of the ovary and have also been reported in conjunction with ovarian carcinosarcoma (Ardighieri et al., 2016; Carlson et al., 2008). The rates of germline mutations in ovarian carcinosarcoma patients have been reported as 20 %, while up to 78 % of cases may contain biallelic somatic mutations in germline driver genes, including *BRCA1* and *BRCA2* (Sia et al., 2023). PARPi have been extensively studied in the context of ovarian carcinoma, particularly in HGSOC patients with both germline and somatic *BRCA* mutations. They have shown efficacy as maintenance therapy in HGSOC patients with *BRCA* mutations, leading to prolonged progression-free survival and clinically meaning improvements in long term overall survival when given after first-line therapy (67 % at 7 years) (Moore et al., 2018; DiSilvestro et al., 2023). However, previous studies primarily focused on HGSOC and did not include carcinosarcoma when investigating the efficacy of PARPi in ovarian cancer maintenance therapy for patients with *BRCA* mutations (Tew et al., 2020).

Preclinical findings suggest that PARPi may be effective in treating OCS, which exhibits homologous recombination deficiency and *BRCA* mutations (Tymon-Rosario et al., 2022). The successful outcome in this case report contributes to current data supporting the potential benefits of PARPi in the treatment of BRCA-mutated ovarian carcinosarcoma and further research is necessary to evaluate clinical efficacy in this patient population and develop optimal treatment strategies.

In conclusion, the favorable response observed in this patient with *BRCA1*-mutated ovarian carcinosarcoma treated with PARP inhibitor maintenance highlights the potential benefit of this approach in selected *BRCA1* mutated patients with OCS. Continued research and participation in clinical trials are crucial to optimize treatment strategies and

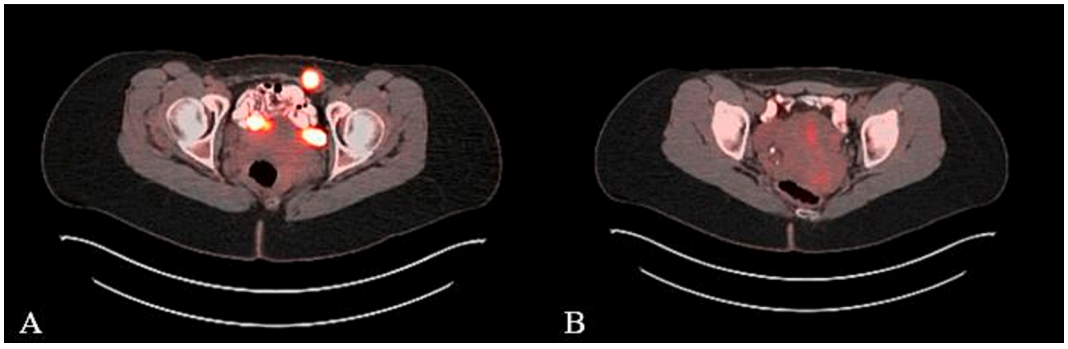

Fig. 1. Left panel (A) shows an intense FDG uptake associated with a single 2.4 x 2.3 cm single enlarged lymph node/metastatic deposit in the medial left inguinal region with an SUV max of 21.7. The right panel (B) demonstrates a linear focus of mild to moderate uptake in the uterus, with an SUV max of 5.7. No definite FDG-avid primary tumor site or additional sites of metastatic disease are identified.

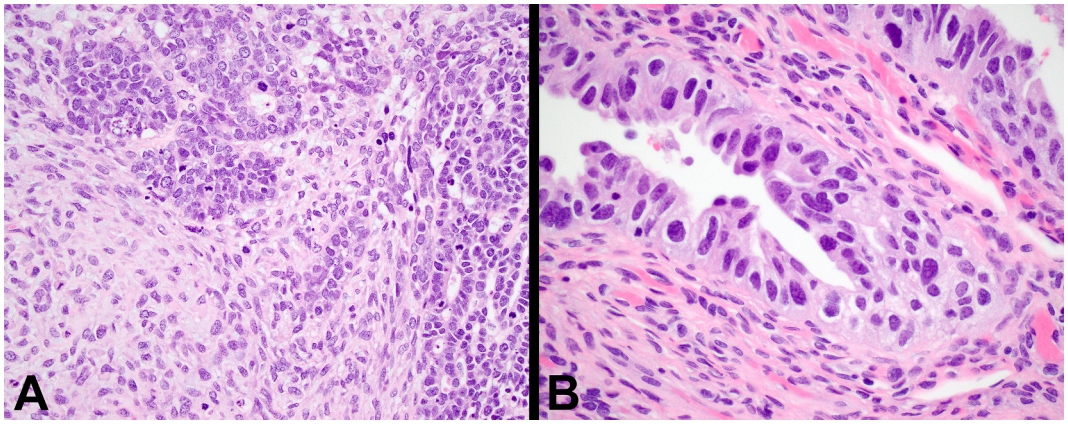

Fig. 2. The left panel (A) shows neoplastic epithelium forming gland at the top and left, as well as neoplastic mesenchyme with focal chondroid differentiation. The right panel (B) shows atypical non-ciliated epithelium with increased intraepithelial architectural complexity without stromal invasion. These features are diagnostic for metastatic heterologous Mullerian carcinosarcoma and serous tubal intraepithelial carcinoma.

improve clinical outcomes for patients with *BRCA*-mutated ovarian carcinosarcoma.

Consent

This project was approved by the Brigham and Women's Hospital Institutional Review Board, Protocol #2008P001632 with Brigham Health Consent Form for Publication.

Informed patient consent was obtained prior to publication of this manuscript.

Author contributions

JDSL: This author participated in the design of the report, data curation, data analysis, writing and review of the manuscript.

JL: This author participated in the design of the report and review of the manuscript.

MKA: This author participated in the design of the report and review of the manuscript.

BQ: This author participated in the data curation, data analysis and review of the manuscript.

MRD: This author participated in the design of the report, data analysis, writing and review of the manuscript.

CRediT authorship contribution statement

Jessica D. St. Laurent: Data curation, Investigation, Methodology, Writing – original draft. **Mary Kathryn Abel:** . **Joyce Liu:** Conceptualization, Supervision, Writing – review & editing. **Bradley J. Quade:** Data curation, Investigation, Supervision, Writing – review & editing. **Michelle R. Davis:** Conceptualization, Investigation, Methodology, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Ardighieri, L., Mori, L., Conzadori, S., Bugatti, M., Falchetti, M., Donzelli, C.M., et al., 2016. Identical TP53 mutations in pelvic carcinosarcomas and associated serous tubal intraepithelial carcinomas provide evidence of their clonal relationship. Virchows Arch. 469, 61–69.

Berton-Rigaud, D., Devouassoux-Shisheboran, M., Ledermann, J.A., Leitao, M.M., Powell, M.A., Poveda, A., et al., 2014. Gynecologic Cancer InterGroup (GCIG) consensus review for uterine and ovarian carcinosarcoma. Int. J. Gynecol. Cancer. 24, S55–S60.

Carlson, J.W., Miron, A., Jarboe, E.A., Parast, M.M., Hirsch, M.S., Lee, Y., et al., 2008. Serous tubal intraepithelial carcinoma: its potential role in primary peritoneal serous carcinoma and serous cancer prevention. J. Clin. Oncol. 26, 4160–4165.

DiSilvestro P, Banerjee S, Colombo N, Scambia G, Kim BG, Oaknin A, Friedlander M, Lisyanskaya A, Floquet A, Leary A, Sonke GS, Gourley C, Oza A, González-Martín A, Aghajanian C, Bradley W, Mathews C, Liu J, McNamara J, Lowe ES, Ah-See ML, Moore KN; SOLO1 Investigators. Overall Survival With Maintenance Olaparib at a 7-Year Follow-Up in Patients With Newly Diagnosed Advanced Ovarian Cancer and a BRCA Mutation: The SOLO1/GOG 3004 Trial. J Clin Oncol. 2023 Jan 20;41(3):609-617. doi: 10.1200/JCO.22.01549. Epub 2022 Sep 9. PMID: 36082969; PMCID: PMC9870219.

Mano, M.S., Rosa, D.D., Azambuja, E., Ismael, G., Braga, S., D'Hondt, V., et al., 2007. Current management of ovarian carcinosarcoma. Int. J. Gynecol. Cancer. 17, 316–324.

Moore, K., Colombo, N., Scambia, G., Kim, B.-G., Oaknin, A., Friedlander, M., et al., 2018. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N. Engl. J. Med. 379, 2495–2505.

Pennington, K.P., Walsh, T., Harrell, M.I., Lee, M.K., Pennil, C.C., Rendi, M.H., et al., 2014. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. Clin. Cancer Res. 20, 764–775.

Ripamonti, B., Manoukian, S., Peissel, B., Azzollini, J., Carcanqiu, M.L., Radice, P., 2018. Survey of gynecological carcinosarcomas in families with breast and ovarian cancer predisposition. Cancer Genetics. 221, 38–45.

See, S.H.C., Behdad, A., Maniar, K.P., Blanco Jr., L.Z., 2019. Ovarian Carcinosarcoma and Concurrent Serous Tubal Intraepithelial Carcinoma With Next-Generation Sequencing Suggesting an Origin From the Fallopian Tube. Int. J. Surg. Pathol. 27, 574–579.

Sia, T.Y., Gordhandas, S.B., Birsoy, O., Kemel, Y., Maio, A., Salo-Mullen, E., et al., 2023. Germline drivers of gynecologic carcinosarcomas. Gynecol. Oncol. 174, 34–41.

Tew, W.P., Lacchetti, C., Ellis, A., Maxian, K., Banerjee, S., Bookman, M., et al., 2020. PARP Inhibitors in the Management of Ovarian Cancer: ASCO Guideline. J. Clin. Oncol. 38, 3468–3493.

Tymon-Rosario, J.R., Manara, P., Manavella, D.D., Bellone, S., Hartwich, T.M.P., Harold, J., et al., 2022. Homologous recombination deficiency (HRD) signature-3 in ovarian and uterine carcinosarcomas correlates with preclinical sensitivity to Olaparib, a poly (adenosine diphosphate [ADP]- ribose) polymerase (PARP) inhibitor. Gynecol. Oncol. 166, 117–125.