Gynecologic Oncology Reports 53 (2024) 101406

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

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

Site-agnostic PARP-inhibitor maintenance therapy of advanced stage *BRCA2*-mutated gastric-type endocervical adenocarcinoma: A case report

Lauren Jill Tostrud [a], Sahana Somasegar [b], Malte Renz [c,d,*]

[a] Department of Obstetrics & Gynecology, Stanford University School of Medicine, Palo Alto, CA, United States
[b] Gynecologic Oncology Division, Stanford University School of Medicine, Palo Alto, CA, United States
[c] Stanford University, Stanford, CA, United States
[d] Department of Obstetrics & Gynecology, Heinrich-Heine University Düsseldorf, Germany

ARTICLE INFO

Keywords:
Site-agnostic use
PARP-inhibitors
Gastric-type endocervical adenocarcinoma

1. Introduction

Gastric-type endocervical adenocarcinomas (GEA) are rare and account for about 10 % of cervical adenocarcinomas (Park, 2020). The overall incidence of cervical adenocarcinomas, however, has been rising (Smith et al., 2000; van der Horst et al., 2017), and GEAs can account for up to 25% of adenocarcinomas in certain populations, including in Japan (Coons et al., 1942). GEAs are HPV-independent cervical cancers and aggressive tumor types (Cree et al., 2020). They can be associated in up to 10% with somatic or germline *STK11* mutations in the setting of Peutz-Jeghers syndrome (Gordhandas et al., 2022). Other reported somatic mutations include *ERBB2* and *KRAS* (Park et al., 2021; Selenica et al., 2021), which may be actionable molecular targets (Ehmann et al., 2022). PARP-inhibitors show well documented efficacy in the maintenance treatment of cancers with increased heritable risk such as *BRCA*-associated ovarian cancer. The sensitivity to PARP-inhibitors in non-*BRCA* associated cancers may be limited. *BRCA* mutations in those cancers could be downstream effects and not the driver mutations (Jonsson et al., 2019). However, clinical data in this area is sparse. Here, we present a patient with a rapidly progressing advanced stage GEA harboring a somatic *BRCA2* mutation whose growth stalled with the site-agnostic use of *olaparib* maintenance therapy.

2. Case

This 50-year-old patient with no pertinent medical or family history presented to her local Gynecologist with a longstanding history of heavy menstrual bleeding and dysmenorrhea. On physical exam, an enlarged 16–18-week size uterus was noted and a normal appearing cervix with a smooth surface. Pelvic ultrasound showed a 12.8 cm posterior fibroid. Definitive surgical management was recommended. Prior to the scheduled surgery, the patient presented to the emergency department with acute right lower quadrant pain. Pelvic ultrasound demonstrated an expanded endometrial cavity with fluid and blood products suspicious for cervical stenosis. CT abdomen/pelvis showed a cervical mass and markedly enlarged uterus. Follow-up MRI pelvis showed a 4.8 cm lower uterine segment/ cervical mass, no parametrial invasion or lymphadenopathy (Fig. 1**A**). A Pap smear showed an adenocarcinoma, favor endometrial origin, and a cervical biopsy showed a p53 mutated endometrial adenocarcinoma. For a presumed endometrial primary with cervical invasion, an exploratory laparotomy, modified radical hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic sentinel lymph node injection and biopsy were performed. On abdominal survey no suspicious pelvic or abdominal lymphadenopathy or any extrauterine disease were noted. Final pathology showed an HPV-independent, gastric type endocervical adenocarcinoma of about 5 × 2.6 cm in size with cervical stroma invasion into the deep third, right parametrial invasion, and involvement of the upper vagina. Margins were close with < 1 mm. p53 and *BRCA2* were mutated, PD-L1 positive (CPS 10 %, TPS 5 %). Given the change in pathological diagnosis, a PET/CT was performed and showed a new, intensely hypermetabolic metastatic left common iliac lymph node (1.8 cm with maximum SUV 14.8) and a new,

* Corresponding author at: Moorenstrasse 5, 40225 Düsseldorf, Germany.
E-mail addresses: renzmalt@stanford.edu, malte.renz@med.uni-duesseldorf.de (M. Renz).

https://doi.org/10.1016/j.gore.2024.101406
Received 2 April 2024; Received in revised form 29 April 2024; Accepted 30 April 2024
Available online 1 May 2024

intensely hypermetabolic left *para*-aortic retroperitoneal lymph node (1.4 cm, maximum SUV 13.6) (Fig. 1**B**). The consensus recommendation of the institutional Tumor Board was for chemoradiation with external beam radiation and weekly cisplatin for 6 cycles followed by vaginal brachytherapy. Post-treatment imaging demonstrated no evidence of residual disease.

Germline testing was performed and negative. Given the somatic *BRCA2* mutation, a site-agnostic trial of maintenance treatment with the PARP inhibitor *olaparib* was considered. The following aspects were discussed with the patient; (i) the aggressive nature of the GEA, which showed rapid progression within the 4 weeks between surgery and repeat imaging after surgery, (ii) the limited therapeutic tools once the disease recurs, (iii) the biological rationale for a PARP-inhibitor maintenance treatment attempt, (iv) the limited clinical data on PARP-inhibitor maintenance in this setting, and (v) possible side effects of PARP-inhibitors. Through shared decision making, the patient decided on an off-label treatment trial with *olaparib*, which was initiated 6 weeks after the completion of brachytherapy. Given the rapidity of the initial tumor growth, surveillance PET imaging was performed every 3 months. The patient tolerated the *olaparib* treatment well with no side effects. Six

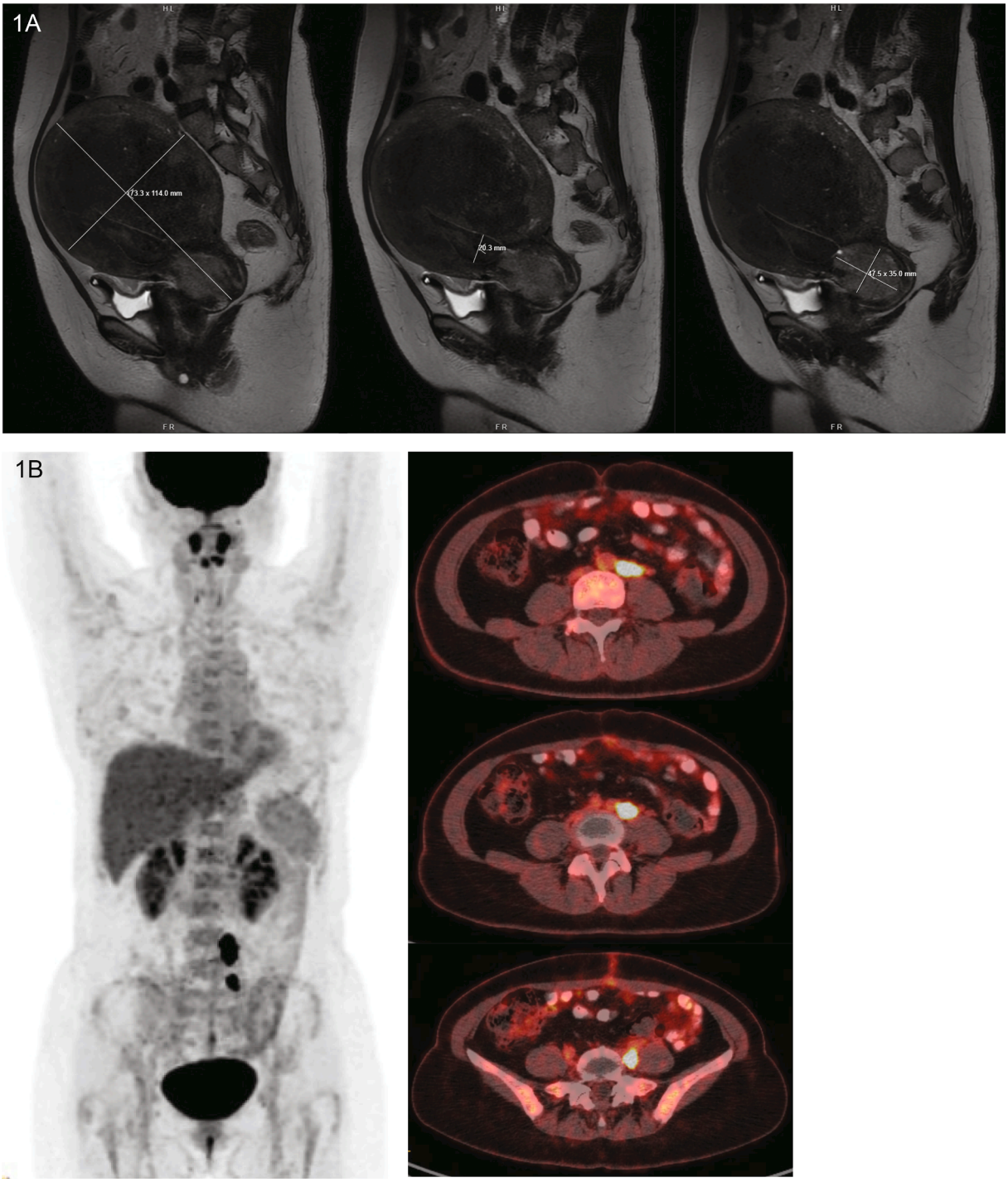

Fig. 1. A: Sagittal pelvic MRI images show the extend of intracervical/ lower uterine segment disease with no apparent surface contour involvement. **B:** Post-operative PET/ CT imaging demonstrates enlarged and hypermetabolic left pelvic (1.4 × 1.3 cm, SUV max 13.6) and *para*-aortic lymphadenopathy (1.8 × 1.1 cm, SUV max 14.8).

months after treatment initiation, a surveillance PET/CT demonstrated an isolated 4 mm right upper lobe pulmonary nodule with mild metabolic activity (SUV 1.5). A CT chest showed only this 4.5 × 3.5 mm nodule and no other suspicious lung nodules. Because of the small size, CT-guided biopsy was not possible. The patient remained on *olaparib* treatment. Repeat PET/CT and CT chest imaging three months later showed no change in size but a mild increase in FDG avidity (SUV 3.2) and no other sites of disease (Fig. 2). The patient was referred to Thoracic Oncology and underwent a bronchoscopy and right thoracoscopic segmentectomy. Final pathology showed a sub-centimeter lesion consistent with metastatic adenocarcinoma of gynecologic origin. The patient has remained on *olaparib* maintenance treatment and continued 3-monthly PET/ CT scans. To-date, 9 months after the thoracoscopic surgery, the patient is doing well with no evidence of disease.

3. Discussion

GEAs reportedly have a significantly poorer prognosis than other cervical adenocarcinomas. The available data is limited to small series. Kojima et al documented in a series of 53 patients with GEA an overall 5-year survival of 30% for GEA versus 77% for non-gastric cervical adenocarcinomas and a 4.5-fold increased risk of recurrence compared to non-gastric adenocarcinomas (Kojima et al., 2007). In a multivariate analysis, gastric type and parametrial invasion were independent predictors of recurrence. GEA typically presents at higher stages and shows an early tendency to peritoneal and omental spread (Karamurzin et al., 2015). In another series of 14 patients with GEA, the median overall survival for advanced stage disease was 12 months (Tremblay et al., 2023). In a more recent series, the progression-free survival for stages II-IV was 17 months (Ehmann et al., 2022).

Various studies reported a 3–4-fold increased risk for cervical cancer in *BRCA* germline mutation carriers (Johannsson et al., 1999; Thompson et al., 2002; Rhiem et al., 2007), especially for *BRCA2* (Momozawa et al., 2022). In our patient, only a somatic *BRCA2* frameshift mutation was found. Epigenetic changes of the *BRCA* genes have been noted in cervical cancer, including promoter hypermethylation and thus silencing. Hypermethylation was found to be more frequent in advanced stages of cervical cancer and predicted worse outcome (Narayan et al., 2003). These findings may make a case for a role of *BRCA* as driver mutation in some cervical cancers.

The efficacy of PARP-inhibitors has been well documented in the BRCA-associated tumors ovarian, breast, prostate, and pancreatic cancer, and FDA-approval has been granted in these cancers. Given the results in ovarian, breast, prostate, and pancreatic cancer, experts in the field have been considering tumor-site agnostic approval for PARP-inhibitors (Markman, 2019), analogous to *pembrolizumab,* the first drug that received tumor site-agnostic FDA approval in May 2017 based on 5 single-arm studies (Le et al., 2015). PARP-inhibitors, however, appear to be increasingly less effective in the order of the *BRCA*-associated tumors mentioned above. While in ovarian and prostate cancer, PARP-inhibitors demonstrated efficacy in BRCA-associated tumors with germline and somatic mutations, few is known about the clinical benefit of PARP-inhibitors in non-*BRCA*-associated cancers with somatic *BRCA* mutations. Somatic mutations of *BRCA* may not result in homologous recombination deficiency as assessed by functional surrogate tests such as HRD testing. It has been hypothesized that in these circumstances somatic *BRCA* mutations may be downstream effects rather than driver mutations and targeting them with PARP-inhibitors may be of limited therapeutic benefit (Jonsson et al., 2019). However, clinical data remains sparse and the few existing case numbers are too small to draw statistically relevant conclusions (Gross and Spencer, 2022). PARP-inhibition has been reported to be beneficial in a small series of uterine sarcomas with somatic *BRCA* mutations (Jonsson et al., 2019). A recent small study of 30 solid tumors suggested that patients with limited treatment options may benefit from PARP-inhibitors. Only 6 tumors in this series showed a *BRCA* mutation, and 6 additional tumors had mutations in the homologous recombination pathway. Patients with the longest disease-free survival of 48 and 24 months harbored somatic *BRCA* mutations in a spindle cell sarcoma and extrahepatic cholangiocarcinoma (Wasef et al., 2022).

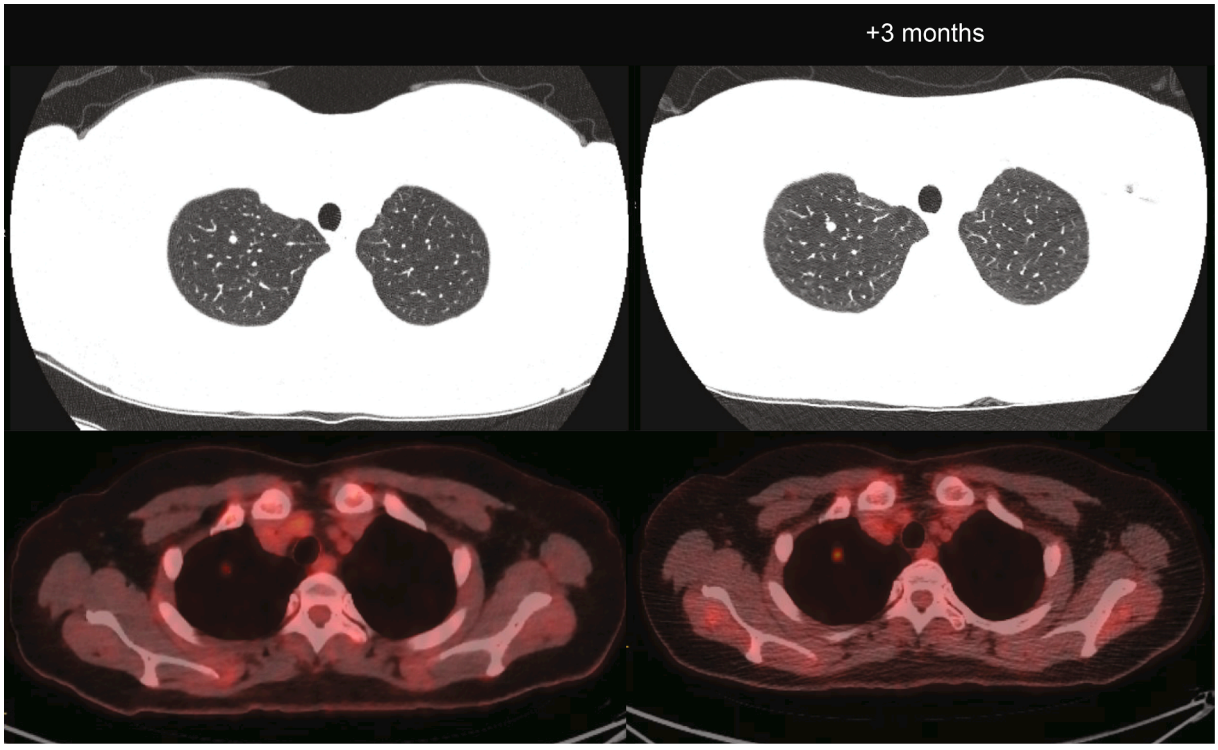

Fig. 2. PET and CT chest imaging of a solitary lung nodule over 3 months; its size remained relatively unchanged of about 4 mm with a mild SUV max increase from 1.5 to 3.2.

An alternative therapy and maintenance strategy might be the combination of *pembrolizumab* with chemoradiation, followed by *pembrolizumab* maintenance as studied in the Keynote-A18 trial (Lorusso et al., 2024). However, the KN-A18 data was not available at the time of chemoradiation treatment for this patient. Additionally, GEA was not included in the trial and patients who had a prior hysterectomy were not eligible.

In the patient presented here, GEA showed initially rapid progression with positive parametrial involvement but no pathologically enlarged lymph nodes at the time of surgery. The patient developed bulky lymphadenopathy in the time between surgery and postoperative PET imaging within 4 weeks. In comparison the isolated subcentimeter lung nodule did not grow significantly but showed a mild increase in FDG-uptake over 3 months; no other new foci appeared over the course of the 16-months course of PARP-inhibitor treatment thus far, i.e., up to the time of publication. Given the nature of a case report, it cannot be ascertained if this effect is due to PARP-inhibitor maintenance therapy since there was no comparison to no PARP-inhibitor treatment; however, there was an apparent significant change in the dynamics of this highly aggressive disease. While the sub-centimeter lung nodule may have been slowly increasing in metabolic activity while on the PARP-inhibitor treatment, the treatment has stalled and slowed disease progression significantly. Because it was an isolated subcentimeter focus, which could be addressed with local surgery, other systemic treatment options were spared for a possible more systemic spread with multiple disease sites. Furthermore, the patient is feeling well, traveling, working, and tolerating the PARP-inhibitor maintenance treatment without any side effects. Given the scarcity of effective therapeutic tools for HPV-independent mucinous cervical adenocarcinomas, PARP-inhibitors appear to be a valid site-agnostic treatment in cases where a somatic *BRCA* mutation is detected.

4. Conclusions

Given limited treatment options and overall poor prognosis of GEA, testing for somatic *BRCA* mutations and maintenance treatment with PARP-inhibition can be considered.

Prior presentation

None.

Patient consent

Written informed consent was obtained from the patient for publication of this case report and the imaging. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Funding

Stanford Cancer Institute [Grant # 1252052-100-WXDJA].

CRediT authorship contribution statement

Lauren Jill Tostrud: Writing – original draft, Investigation, Data curation. **Sahana Somasegar:** Writing – review & editing, Investigation. **Malte Renz:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization.

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.

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