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Case report

Durable response to hormonal therapy in a patient with rapidly progressive low-grade serous ovarian cancer: A case report

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ABSTRACT

This case report describes a 46-year-old patient with rapidly progressive stage IIIA1 estrogen receptor positive low grade serous ovarian cancer (LGSC). She was optimally debulked with no residual disease and received three cycles of adjuvant liposomal doxorubicin and carboplatin intravenous chemotherapy. CT scan and pelvic exam after her third cycle revealed a 5.7 cm nodular fixed left vaginal cuff mass involving the rectosigmoid consistent with rapidly progressive disease on chemotherapy. The decision was made to initiate letrozole, and she demonstrated a prolonged partial response for 34 months on hormonal therapy. The optimal management of newly diagnosed LGSC has yet to be determined. This unique case suggests that patients with newly diagnosed disease will not be compromised if treated with adjuvant hormonal monotherapy.

1. Introduction

Low grade serous ovarian carcinoma (LGSC) accounts for approximately 5–10% of serous epithelial ovarian cancers and is characterized by a unique molecular profile and clinical course when compared to its high-grade counterpart. Several retrospective studies have demonstrated the relative chemoresistance of LGSC (Gershenson et al., 2006, 2009). Gershenson et al. demonstrated that 62% of women with primary LGSC treated with standard platinum-based chemotherapy had persistent disease at the time of second-look surgery (Gershenson et al., 2006). Moreover, response rates are strikingly lower in women with advanced LGSC compared to women with high-grade serous cancers; only 23% of patients with suboptimally debulked disease responded to adjuvant platinum-based chemotherapy (Gershenson et al., 2009).

This relative chemotherapy resistance has prompted investigation into alternate therapies. Interestingly, LGSC is more frequently estrogen and progesterone positive when compared to other histologies (Escobar et al., 2013), and hormonal therapy is often used in the recurrent setting and as maintenance therapy (Gershenson et al., 2012, 2017). LGS tumors also often exhibit *RAS-RAF-MAPK* mutations, and MEK inhibitors have shown promising results (Gershenson et al., 2019a, 2019b). In the MILO trial, the *MEK* inhibitor, binimetinib, demonstrated a similar progression free survival (PFS) when compared to standard of care chemotherapy (10.4 vs 11.5 months) in patients with recurrent or persistent LGSC. However, longer PFS (17.7 vs 10.8 months) was noted among patients with *KRAS*-mutated tumors treated with binimetinib (Lastname et al., 2019). Bevacizumab, an anti-angiogenic agent that targets VEGF, has also demonstrated anti-tumor activity in LGSC (Grisham et al., 2014).

The optimal management of women with newly diagnosed advanced disease remains controversial. Because of the relative chemoresistance of LGSC and the benefit of hormonal treatment in both maintenance and recurrent settings, there is growing interest in the use of front-line hormonal monotherapy. Fader and colleagues treated women with newly diagnosed LGSC (stage II–IV) with primary hormonal therapy (Fader et al., 2017). The majority of patients were treated with aromatase inhibitors. The three-year progression-free and overall survival rates were 79.0% and 93.1%, respectively, suggesting that adjuvant hormonal monotherapy could avoid chemotherapy toxicities without compromising patient survival outcomes (Fader et al., 2017). Here, we present a patient with LGSC who rapidly progressed on platinum-based therapy and demonstrated prolonged partial response with an aromatase inhibitor, illustrating the potential of hormonal therapy in the front-line setting.

2. Case report

A premenopausal patient was initially seen in November 2016 for

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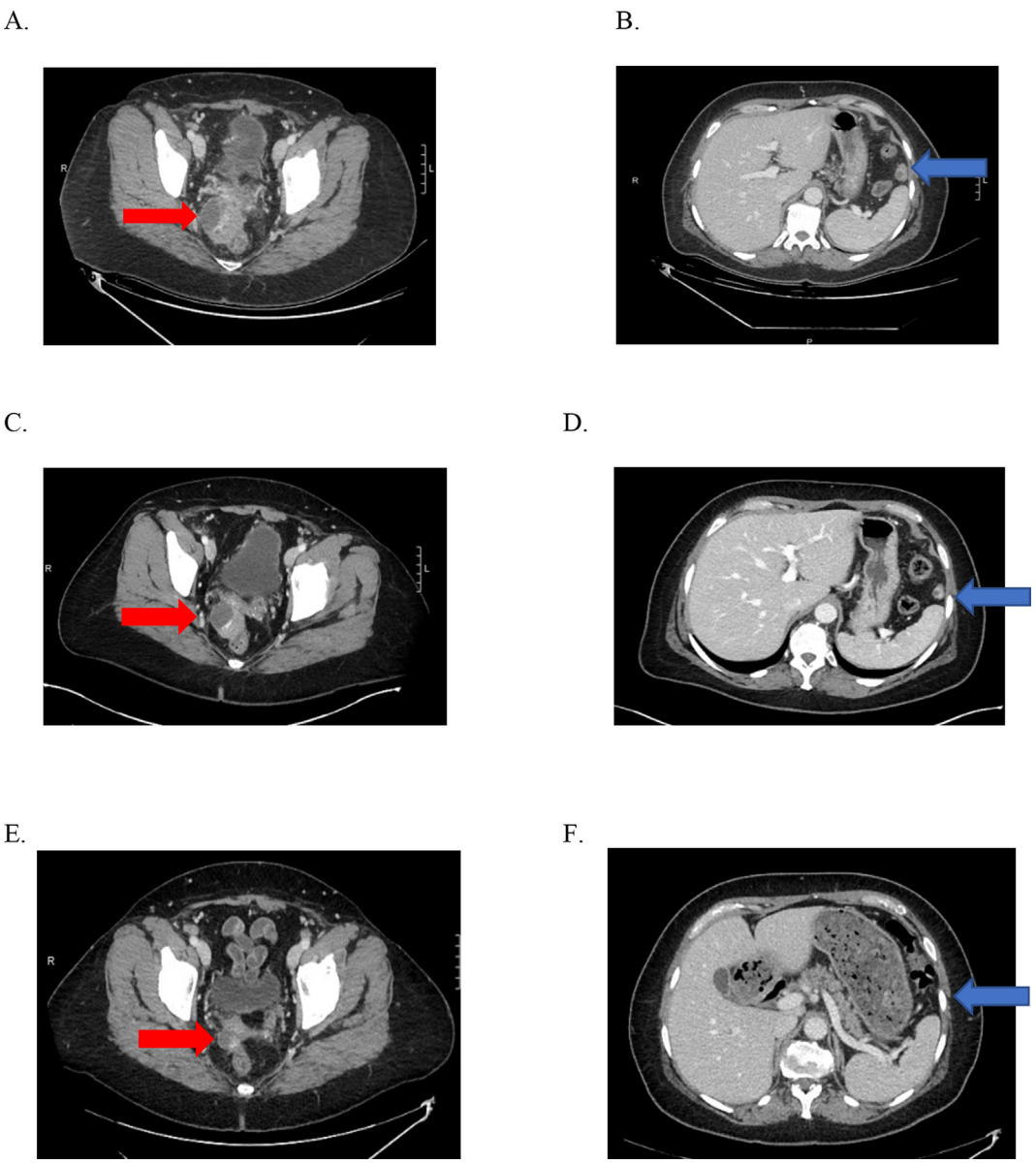

Fig. 1. The figure represents images from abdomen and pelvic CT scans. At the time of initial progression (4/2017) images demonstrated disease recurrence with a (A) 5.7 cm perirectal (red arrow); (B) 2.2 cm left perisplenic nodule (blue arrow). After 2 months of letrozole therapy the (C) perirectal mass measured 3.9 cm (green arrow); and (D) left perisplenic nodule 1.7 cm (blue arrow). Scans on 7/2019 demonstrated the nadir measurement after 27 months of letrozole therapy, with greatest dimension of perirectal mass measuring 1.9 cm (E). The left perisplenic nodule had resolved (F). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

pelvic pain and diagnosed with a 5.5 cm complex, lobulated partially cystic mass in the right adnexa, as well as possible periaortic adenopathy based on CT scan. Her preoperative CA-125 was 164.6. She also had recent breast and colon screening that was negative for malignancy, and her family history was negative for any gynecologic, breast or gastrointestinal cancers.

After consultation with the gynecologic oncology division, she underwent a robotic-assisted total laparoscopic hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, right pelvic and para-aortic lymph node dissection and peritoneal biopsies on 12/12/2016. She had no gross residual disease at surgical completion. Final pathology showed an estrogen receptor positive, stage IIIA1 low grade serous ovarian cancer with para-aortic lymph node positive for metastasis and right ovarian and right pelvic and cul-de-sac peritoneal biopsies positive for metastatic adenocarcinoma.

Adjuvant chemotherapy was initiated with carboplatin AUC 5 and liposomal doxorubicin 30 mg/m^2 as she was adamant about avoiding paclitaxel and alopecia. She completed three cycles of chemotherapy on 3/14/17. A CT scan on 4/7/2017 was concerning for pelvic recurrence, with a 5.7 cm perirectal mass and a 2.2 cm perisplenic lesion [Fig. 1A and B]. Pelvic exam findings revealed a nodular fixed vaginal cuff mass involving the rectosigmoid. She initiated hormonal therapy with letrozole 2.5 mg daily. Repeat imaging on 6/27/2017 revealed decreased disease size of the perirectal mass, now measuring 3.9 cm, and the perisplenic lesion, now measuring 1.7 cm [Fig. 1C and D]. The lesions continued to decrease in size. Repeat CT scan on 7/29/19 demonstrated complete resolution of the perisplenic lesion and decrease in the perirectal mass to 1.9 cm [Fig. 1E and F]. Her physical exam was notable for a completely smooth vaginal apex, and no evidence of residual mass. She remained without evidence of progression until pelvic exam and repeat CT on 2/4/2020 showed a perirectal mass measuring 3.7 cm. No other sites of metastatic disease were identified.

Regarding adverse effects related to long-term use of letrozole, she reported minimal side effects throughout her treatment. Her bone

density scan was notable for decreased bone density approximately 18 months after initiating letrozole, and she was started on calcium and vitamin D. During her therapy she was able to work full time and had excellent quality of life.

Written, informed consent to present the case was obtained from the patient.

3. Discussion

Our case illustrates a durable partial response of almost three years to aromatase therapy in a patient with rapidly progressive disease while receiving front-line platinum-based therapy for advanced stage disease. Interest in the use of front-line aromatase therapy for LGSC is increasing based on the retrospective data in newly diagnosed disease as well as in the maintenance and recurrent settings (Gershenson et al., 2012, 2017).

Gershenson et al. reported promising results with hormonal maintenance therapy compared to surveillance following primary treatment in a retrospective cohort at MD Anderson Cancer Center (Gershenson et al., 2017). Over 200 patients with newly diagnosed stage II-IV LGSC underwent primary cytoreductive surgery followed by platinum-based chemotherapy were included. Seventy patients received hormonal therapy, while 133 underwent active surveillance only. Maintenance hormonal therapies included letrozole (54%), tamoxifen (29%), leuprolide acetate (6%), and anastrozole (3%). Overall, patients on hormonal therapy had approximately 55% reduction in the risk of disease progression compared to those observed (64.9 vs 26.4 months; HR = 0.44; 95% CI, 0.31, 0.64; $p < .001$). When stratified by disease status, persistent (38.1 vs 15.2 months) and complete remission (81.1 vs 30 months), the PFS advantage remained for those treated with hormonal therapy (Gershenson et al., 2017).

Fader and colleagues conducted the first study that examined the use of hormonal monotherapy for women with newly diagnosed LGSC after primary cytoreductive surgery (stage II–IV) (Fader et al., 2017). Twenty-seven patients participated in this study and 25 of these (93%) had advanced stage disease. Over 90% of these patients received an aromatase inhibitor; the three-year progression-free and overall survival rates were 79.0% and 93.1%, respectively. These findings are comparable to prior populations who received front-line platinum based chemotherapy. Recent National Comprehensive Cancer Network (NCCN) guidelines for LGSC (version 1.2020), include front-line chemotherapy followed by observation or hormonal maintenance, or primary hormonal therapy for women with newly diagnosed stage II-IV LGCS (National Comprehensive Cancer Network, 2020).

The NCCN guidelines include the following hormonal therapies as treatment options for LGSC: aromatase inhibitors including anastrozole, letrozole, and exemestane; leuprolide acetate; and the SERM, tamoxifen (National Comprehensive Cancer Network, 2020). The majority of patients in the Gershenson et al. maintenance study received aromatase inhibitors; however, the study was not designed to draw conclusions about optimal hormonal regimen (Gershenson et al., 2017). In a recurrent disease setting, 7 of 8 patients who had a complete or partial response received an aromatase inhibitor (Gershenson et al., 2012). In the Fader study, the majority of physicians selected letrozole as their hormonal agent of choice. The preference for letrozole was attributed to the positive prior maintenance findings and superiority of aromatase inhibitors in the suppression of estradiol in breast cancer patients (Fader et al., 2017). Letrozole demonstrated higher response rates compared to tamoxifen in the GOG 281 randomized phase II/III clinical trial comparing the efficacy of trametinib versus standard of care in patients with recurrent or progressive LGSC. In this study, letrozole achieved a 13.6% objective response rate, compared to a 0% objective response rate in patients treated with tamoxifen (Lastname et al., 2019). While this assessment was not an endpoint of the study, the response data suggests that aromatase inhibitors may be more effective than tamoxifen in recurrent/progressive LGSC.

Currently, the NRG-GY019 randomized phase III trial comparing combination paclitaxel and carboplatin chemotherapy followed by maintenance letrozole to letrozole monotherapy in patients with stage II-IV LGSC is ongoing (NCT #04095364). The objective of this study is to compare the efficacy of standard chemotherapy followed by letrozole maintenance to letrozole monotherapy. The study also includes important endpoints regarding the association between estrogen receptor expression and pathway mutations and treatment response, as well as an assessment of patient-reported outcomes. Patient-reported outcomes are a crucial aspect of treatment evaluation. Our patient continues to work full time in a very active position, and maintaining her quality of life, minimizing side effects of chemotherapy, and avoiding alopecia was and continues to be extremely important to her.

Our case report demonstrates that aromatase inhibitor use in LGSC was more beneficial than traditional platinum-based therapy in terms of disease control. The findings from the ongoing NRG-GY019 trial comparing chemotherapy followed by aromatase inhibitor maintenance versus aromatase inhibitor alone will hopefully provide definitive results to direct therapy in women with newly diagnosed LGSC. More research will still be needed to identify optimal hormonal regimens and explore combinations with novel agents and the potential benefits of adding MEK and VEGF inhibitors to front-line therapy.

CRediT authorship contribution statement

Catherine H. Watson: Conceptualization, Data curation, Writing - original draft. **Angeles Alvarez Secord:** Conceptualization, Writing - review & editing.

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