Gynecologic Oncology Reports 38 (2021) 100877

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

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

Progestin and aromatase inhibitor therapy in recurrent, estrogen/progestin receptor positive uterine carcinosarcoma: A case report

Angela L. Liang [a], Payam Katebi Kashi [a], Mark Hopkins [b], Anna Beavis [a], Stephanie Gaillard [a,c], Ie-Ming Shih [b], Amanda N. Fader [a,*]

[a] The Kelly Gynecologic Oncology Service, Department of Gynecology and Obstetrics, Johns Hopkins School of Medicine, Baltimore, MD 21287, United States
[b] Department of Pathology, Johns Hopkins School of Medicine, Baltimore, MD 21287, United States
[c] Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins School of Medicine, Baltimore, MD 21287, United States

ARTICLE INFO

Keywords
Uterine carcinosarcoma
Hormone receptors
Aromatase inhibitors
Progestin therapy

1. Introduction

Uterine carcinosarcoma (UCS), previously known as malignant mixed mesodermal tumor (MMMT), is an aggressive subtype of endometrial cancer. UCS represents less than 5% of uterine tumors but accounts for 15% of deaths caused by uterine malignancies (Cantrell et al., 2015). The overall survival (OS) rate at five years is 59% for stages I-II, 22% for stage III, and 9% for stage IV (Cantrell et al., 2015).

Previously classified as sarcomas, it is now recognized that UCS tumors are likely epithelial tumors that have undergone mesenchymal differentiation. The carcinomatous component of these tumors is typically high-grade, such as serous or clear cell. The sarcomatous component can be homologous, including leiomyosarcoma or endometrial stromal sarcoma, or heterologous, such as rhabdomyosarcoma or osteosarcoma. The estrogen receptor (ER) positivity rates are typically low, between 23% and 33% (de Jong, 2011; Koivisto-Korander, 2011); one study noted that only 8% of tumors demonstrated estrogen/progesterone (ER/PR) receptor expression in both the epithelial and mesenchymal component (de Jong, 2011). Of note, there are data to suggest increased survival advantage in hormone-positive UCS (Huang et al, 2007; Koivisto-Korander, 2011).

The preferred treatment for UCS consists of surgery followed by adjuvant carboplatin plus paclitaxel and radiation therapy. Radiation therapy may improve local control in early-stage disease but does not decrease distant metastases or OS (Callister et al., 2004). A phase III trial reported that carboplatin plus paclitaxel resulted in progression-free survival (PFS) of 13 months and OS of 37 months (Miller et al., 2020). Ifosfamide, while effective, is considered quite toxic when administered with cisplatin or paclitaxel, and many other chemotherapy agents have little demonstrable benefit (Cantrell et al., 2015).

Hormonal agents are routinely used in the treatment of low-grade endometrial cancer, in which ER/PR positivity are present in up to 90% of cases (Shen et al., 2017). Progestin therapy is often used to treat low-grade endometrial cancer in women who wish to preserve fertility, with response rates ranging from 66% (Hahn et al., 2009) to 86% (Eftekhar et al., 2009). Aromatase inhibitors with and without targeted therapy have also shown benefit in multiple case reports of early-stage disease (Gao et al., 2014) and phase II studies in recurrent disease (Slomovitz et al., 2015).

Hormone receptor expression may serve similarly as a therapeutic target in higher-grade endometrial tumors. Our group recently reported long-term disease control in a patient with ER-positive, recurrent uterine serous carcinoma with bone and visceral metastases who received treatment with letrozole and zoledronic acid (Najjar et al., 2020). However, few studies have demonstrated efficacy of hormonal therapy in ER/PR positive UCS. In this case report, we present efficacy of megestrol acetate and letrozole for a woman with ER/PR positive, recurrent UCS.

* Corresponding author at: 600 N Wolfe St, Phipps Bldg, Rm 287, Baltimore, MD 21287, United States.
E-mail address: afader1@jhmi.edu (A.N. Fader).

https://doi.org/10.1016/j.gore.2021.100877
Received 26 June 2021; Received in revised form 5 September 2021; Accepted 9 September 2021
Available online 4 October 2021

2. Case report

A 70-year-old woman with a remote history of breast cancer in 2008 presented with new-onset abdominal pain in 2013. Her past medical history was otherwise unremarkable, and her past surgical history included lumpectomy and cesarean section.

Briefly, the patient's breast cancer history was notable for infiltrating ductal carcinoma with lobular features, grade 3, ER 95%, PR 1%, human epidermal growth factor receptor (HER)-2 negative, and stage pT1cN0. She underwent lumpectomy in 2008 and received four cycles of docetaxel plus cyclophosphamide followed by radiation therapy. She was maintained on letrozole for five years without evidence of disease recurrence by annual mammography and clinical examination.

Prompted by her new-onset abdominal pain in 2013, the patient received transvaginal ultrasound imaging, which revealed a complex cystic mass, and pelvic magnetic resonance imaging (MRI), which illustrated an expanded uterus with frond-like tissue. The patient underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy, and pelvic and *para*-aortic lymphadenectomy. Pathology identified carcinosarcoma with myometrial invasion (less than50%), and metastatic disease was present in the bilateral ovaries and 8 of 15 pelvic lymph nodes, consistent with International Federation of Gynecology and Obstetrics (FIGO) stage IIIC2 disease (Fig. 1).

The patient subsequently received six cycles of intravenous carboplatin and paclitaxel, 45 Gy of pelvic and paraaortic radiotherapy, and 7 Gy of vaginal brachytherapy. She was followed closely every 3 months with clinical examination and CA-125, and by CT every six months, remaining disease-free for almost four years.

Forty-four months after surgery, her CA-125 levels increased and positron emission tomography (PET)-CT revealed a 1.3 cm, metabolically hyperactive, aortocaval lymph node; CT-guided biopsy confirmed recurrent, ER/PR positive, HER-2 negative adenocarcinoma consistent with the patient's known UCS.

The recurrence appeared to be isolated and slow-growing. The patient was observed closely for 7 months, but the isolated node continued growing. A multidisciplinary tumor board reviewed treatment options of surgery, chemotherapy, and radiation therapy; progestin therapy was recommended with megestrol acetate per oral 80 mg twice daily, given that the patient was asymptomatic, and the recurrence was isolated, and ER/PR positive. PET-CT after ten months on this therapy demonstrated a stable lymph node with no hypermetabolic activity, suggesting possible resolution of the recurrent disease.

Fifteen months into treatment, the patient developed a concurrent deep vein thrombosis (DVT) and pulmonary emboli (PE). Megestrol acetate was paused for one week until after the DVT was extracted via thrombectomy and the patient was started on maximum anticoagulation therapy. Per tumor board recommendation, the patient was restarted on megestrol acetate at a decreased dose of 40 mg twice daily with maximum anticoagulation therapy. However, she experienced recurrent DVT after one month and was thus transitioned to aromatase inhibitor therapy with letrozole per oral 2.5 mg daily. The patient experienced slight interval increase in metabolic activity on PET-CT, though no increase in nodal size or evidence of other disease after ten months on letrozole. She thus underwent stereotactic radiation and thereafter resumed with letrozole therapy.

The patient exhibits no evidence of disease recurrence per her most recent CT after 25 months on letrozole. She also has not experienced treatment toxicity, and her Eastern Cooperative Oncology Group (ECOG) Performance Status remains at 1. She continues on surveillance every six months by PET-CT and clinical examination.

3. Discussion

This case demonstrates long-term disease control of an ER/PR positive, recurrent UCS tumor was successfully achieved through hormonal therapy with megestrol acetate followed by letrozole and stereotactic radiation supplementation.

Megestrol acetate is commonly used to treat low-grade endometrial cancer, especially as fertility-sparing therapy, while more aggressive tumors, such as UCS, are likely to be treated with chemotherapy. In low-

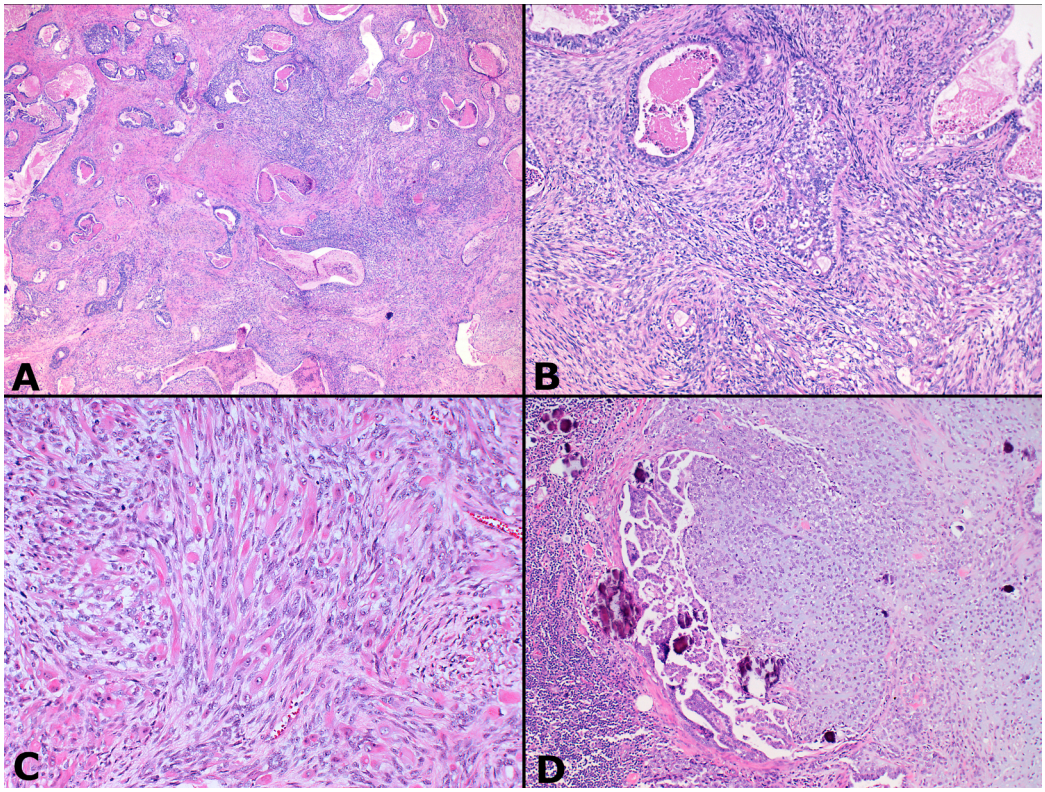

Fig. 1. A) Sections from the uterus showed both a carcinomatous component with endometrioid and clear cell features as well as a sarcomatous component composed of other heterologous and homologous elements (20x, H&E). B) The majority of the mesenchymal component consisted of a non-specific malignant spindle cell sarcoma (40x, H&E). C) Focally, eosinophilic rhabdoid cells were present with fibrillary cytoplasm consistent with rhabdomyosarcoma, a heterologous component (64x, H&E). D) Metastatic carcinosarcoma involving a lymph node. The metastatic tumor demonstrated both a carcinomatous component with prominent papillary architecture and a sarcomatous component with a striking chondromyxoid appearance (40x, H&E).

grade endometrial cancers, which also have high rates of ER/PR positivity, megestrol acetate is highly effective (Qin et al., 2016). This case demonstrates that megestrol acetate may also be effective in more aggressive tumors, particularly those with ER/PR expression. Previous studies provide further evidence consistent with this case. In a phase II study of advanced and recurrent endometrial carcinoma, carboplatin plus sequential hormonal therapy with megestrol acetate and tamoxifen resulted in complete response for 30.8% (4/13) of all patients but 75% (3/4) of ER/PR positive patients (Pinelli et al., 1996). In a phase II trial that only included women with ER-positive advanced endometrial cancer, the response rate was also high at 54.1% (19/35) of patients whose disease had not progressed at 6 months (Pautier et al., 2017). Consistent with this case report, these studies suggest that megestrol acetate may be particularly effective for treating patients with ER/PR positive endometrial cancer, even if advanced or recurrent.

However, this case also exemplifies a significant limitation of megestrol acetate, namely that it predisposes patients to thromboembolic disorders, which this patient experienced and for which this patient was discontinued from megestrol acetate. In the context of cancer patients, a group already susceptible to hypercoagulability, the additional risk from megestrol acetate may result in severe adverse events. In a phase II trial of alternating megestrol acetate and tamoxifen, two of 56 patients experienced a DVT, four experienced a PE, and one experienced a stroke (Fiorica et al., 2004). Another trial of advanced endometrial cancer reported that out of 22 patients treated with temsirolimus plus alternating megestrol acetate and tamoxifen, there were five DVTs, two PEs, one myocardial infection, and one sudden death (Fleming et al., 2014). Thus, while megestrol acetate may benefit patients with ER/PR positive endometrial cancer, patients should also be evaluated for contraindications due to hypercoagulability risk factors, and patients should be considered for concurrent anticoagulation therapy as appropriate.

After being transitioned from megestrol acetate to letrozole and receiving additional SBRT, the patient in this case report achieved long-term disease control for 16 months with minimal treatment toxicity. This is consistent with a case of a patient with hormone receptor positive, recurrent UCS who remained disease-free after five years on letrozole (Martin-Romano et al., 2017). However, the current patient's response to letrozole is notable given that she had been on letrozole maintenance for ductal carcinoma when she was diagnosed with UCS. Previous studies suggest that hormonal therapy for breast cancer may even be a risk factor for developing UCS (Uehara et al., 2012). To our knowledge, this is the first reported case of a patient who responded to hormonal therapy after developing UCS while taking an aromatase inhibitor. In addition, larger studies have reported low response rates to aromatase inhibitor therapy, where anastrozole resulted in an 8.7% RR (2/23) and letrozole resulted in a 9.4% RR (3/32) for advanced or recurrent endometrial carcinoma (Gao et al., 2014). In a trial limited to post-menopausal women with ER/PR positive recurrent endometrial cancer, anastrozole still only yielded a 7% RR (6/82) (Mileshkin et al., 2019). The favorable outcomes in case reports, including this one, may be attributed to publication bias. In addition, the patient in this case report may have also benefited from the more indolent and isolated nature of the patient's recurrence. The additional SBRT that the patient received while on letrozole may have also contributed to the patient's long-term disease control, as SBRT confers a PFS rate at four years of 45% when used to treat isolated *para*-aortic lymph node metastasis in patients with uterine cancer (Choi et al., 2009).

In summary, this case report illustrates the potential benefit of hormonal therapy with progestin and aromatase inhibitor therapy in the management of isolated, ER/PR positive, recurrent uterine carcinosarcoma. While megestrol acetate is mainly used to treat women with low-grade endometrial carcinoma, further studies on megestrol acetate for hormone receptor-positive, high-grade histology endometrial cancer are warranted. Response to megestrol acetate may depend more on the degree and homogeneity of tumoral ER and PR positivity (and other molecular factors) than tumor stage or histology, suggesting that evaluating for ER and PR positivity in the recurrent setting may be beneficial in guiding personalized treatment decisions in women with a variety of endometrial cancer histologies. The long-term disease control demonstrated in this case report suggests that further studies should explore which prognostic factors may best predict patient response to hormonal therapies. Together, these efforts may yield a more targeted and effective approach to treating patients with aggressive uterine carcinosarcoma.

4. Consent statement

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

CRediT authorship contribution statement

Angela L. Liang: Writing – original draft, Project administration. **Payam Katebi Kashi:** Writing – review & editing. **Mark Hopkins:** Writing – review & editing. **Anna Beavis:** Writing – review & editing. **Stephanie Gaillard:** Writing – review & editing. **Ie-Ming Shih:** Writing – review & editing. **Amanda N. Fader:** Conceptualization, Supervision, Writing – review & editing.

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

Callister, M., Ramondetta, L.M., Jhingran, A., Burke, T.W., Eifel, P.J., 2004. Malignant mixed Müllerian tumors of the uterus: analysis of patterns of failure, prognostic factors, and treatment outcome. Int J Radiat Oncol Biol Phys 58 (3), 786–796. https://doi.org/10.1016/S0360-3016(03)01561-X.

Cantrell, L.A., Blank, S.V., Duska, L.R., 2015. Uterine carcinosarcoma: A review of the literature. Gynecol Oncol 137 (3), 581–588. https://doi.org/10.1016/j.ygyno.2015.03.041.

Choi, C.W., Cho, C.K., Yoo, S.Y., Kim, M.S., Yang, K.M., Yoo, H.J., Seo, Y.S., Kang, J.K., Lee, D.H., Lee, K.H., Lee, E.D., Rhu, S.Y., Choi, S.C., Kim, M.H., Kim, B.J., 2009. Image-guided stereotactic body radiation therapy in patients with isolated para-aortic lymph node metastases from uterine cervical and corpus cancer. Int J Radiat Oncol Biol Phys 74 (1), 147–153. https://doi.org/10.1016/j.ijrobp.2008.07.020.

de Jong, R.A., Nijman, H.W., Wijbrandi, T.F., Reyners, A.K., Boezen, H.M., Hollema, H., 2011. Molecular markers and clinical behavior of uterine carcinosarcomas: focus on the epithelial tumor component. Modern Pathology 24, 1368–1379. https://doi.org/10.1038/modpathol.2011.88.

Eftekhar, Z., Izadi-Mood, N., Yarandi, F., Shojaei, H., Rezaei, Z., Mohagheghi, S., 2009. Efficacy of megestrol acetate (megace) in the treatment of patients with early endometrial adenocarcinoma: our experiences with 21 patients. Int J Gynecol Cancer 19 (2), 249–252. https://doi.org/10.1111/IGC.0b013e31819c5372.

Fiorica, J. V., Brunetto, V. L., Hanjani, P., Lentz, S. S., Mannel, R., Andersen, W., & study, G. O. G., 2004. Phase II trial of alternating courses of megestrol acetate and tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol, 92(1), 10-14. https://doi.org/10.1016/j.ygyno.2003.11.008.

Fleming, G.F., Filiaci, V.L., Marzullo, B., Zaino, R.J., Davidson, S.A., Pearl, M., Makker, V., Burke, J.J., Zweizig, S.L., Van Le, L., Hanjani, P., Downey, G., Walker, J. L., Reyes, H.D., Leslie, K.K., 2014. Temsirolimus with or without megestrol acetate and tamoxifen for endometrial cancer: a gynecologic oncology group study. Gynecol Oncol 132 (3), 585–592. https://doi.org/10.1016/j.ygyno.2014.01.015.

Gao, C., Wang, Y., Tian, W., Zhu, Y., Xue, F., 2014. The therapeutic significance of aromatase inhibitors in endometrial carcinoma. Gynecol Oncol 134 (1), 190–195. https://doi.org/10.1016/j.ygyno.2014.04.060.

Hahn, H.S., Yoon, S.G., Hong, J.S., Hong, S.R., Park, S.J., Lim, J.Y., Kwon, Y.S., Lee, I.H., Lim, K.T., Lee, K.H., Shim, J.U., Mok, J.E., Kim, T.J., 2009. Conservative treatment with progestin and pregnancy outcomes in endometrial cancer. Int J Gynecol Cancer 19 (6), 1068–1073. https://doi.org/10.1111/IGC.0b013e3181aae1fb.

Huang, G.S., Chiu, L.G., Gebb, J.S., Gunter, M.J., Sukumvanich, P., Goldberg, G.L., Einstein, M.H., 2007. Serum CA125 predicts extrauterine disease and survival in uterine carcinosarcoma. Gynecol Oncol 107, 513–517. https://doi.org/10.1016/j.ygyno.2007.08.060.

Koivisto-Korander, R., Butzow, R., Koivisto, A.-M., Leminen, A., 2011. Immunohistochemical studies on uterine carcinosarcoma, leiomyosarcoma, and

endometrial stromal sarcoma: expression and prognostic importance of ten different markers. Tumor Biol. 32, 451–459. https://doi.org/10.1007/s13277-010-0138-1.

Martin-Romano, P., Jurado, M., Idoate, M.A., Arbea, L., Hernandez-Lizoain, J.L., Cano, D., Paramo, J.A., Martin-Algarra, S., 2017. Durable complete remission with aromatase inhibitor therapy in a patient with metastatic uterine carcinosarcoma with poor performance status and coagulation disorders: a case report. J Med Case Rep 11 (1), 115.

Mileshkin, L., Edmondson, R., O'Connell, R. L., Sjoquist, K. M., Andrews, J., Jyothirmayi, R., Beale, P., Bonaventura, T., Goh, J., Hall, M., Clamp, A., Green, J., Lord, R., Amant, F., Alexander, L., Carty, K., Paul, J., Scurry, J., Millan, D., Nottley, S., Friedlander, M., & group, P. s., 2019. Phase 2 study of anastrozole in recurrent estrogen (ER)/progesterone (PR) positive endometrial cancer: The PARAGON trial - ANZGOG 0903. Gynecol Oncol, 154(1), 29-37. https://doi.org/10.1016/j.ygyno.2019.05.007.

Miller, D.S., Filiaci, V.L., Mannel, R.S., Cohn, D.E., Matsumoto, T., Tewari, K.S., DiSilvestro, P., Pearl, M.L., Argenta, P.A., Powell, M.A., Zweizig, S.L., Warshal, D.P., Hanjani, P., Carney, M.E., Huang, H., Cella, D., Zaino, R., Fleming, G.F., 2020. Carboplatin and paclitazel for advanced endometrial cancer: Final overall survival and adverse event analysis of a Phase III trial (NRG Oncology/GOG0209). J Clin Oncol 38 (22), 3841–3850.

Najjar, O., Varghese, A., Shahi, M., Vang, R., Gaillard, S., Smith, T., Fader, A.N., 2020. Aromatase inhibitor therapy in recurrent, estrogen-receptor positive uterine serous carcinoma: A case report. Gynecol Oncol Rep 32, 100555. https://doi.org/10.1016/j.gore.2020.100555.

Pautier, P., Vergote, I., Joly, F., Melichar, B., Kutarska, E., Hall, G., Lisyanskaya, A., Reed, N., Oaknin, A., Ostapenko, V., Zvirbule, Z., Chetaille, E., Geniaux, A., Shoaib, M., Green, J.A., 2017. A Phase 2, Randomized, Open-Label Study of Irosustat Versus Megestrol Acetate in Advanced Endometrial Cancer. Int J Gynecol Cancer 27 (2), 258–266. https://doi.org/10.1097/IGC.0000000000000862.

Pinelli, D.M., Fiorica, J.V., Roberts, W.S., Hoffman, M.S., Nicosia, S.V., Cavanagh, D., 1996. Chemotherapy plus sequential hormonal therapy for advanced and recurrent endometrial carcinoma: a phase II study. Gynecol Oncol 60 (3), 462–467. https://doi.org/10.1006/gyno.1996.0074.

Qin, Y., Yu, Z., Yang, J., Cao, D., Yu, M., Wang, Y., Shen, K., 2016. Oral progestin treatment for early-stage endometrial cancer: A systematic review and meta-analysis. Int j Gynecol Cancer 26 (6), 1081–1091.

Uehara, T., Onda, T., Togami, S., Amano, T., Tanikawa, M., Sawada, M., et al., 2012. Prognostic impact of the history of breast cancer and of hormone therapy in uterine carcinosarcoma. Int J Gynecol Cancer. 22 (2), 280–285.

Shen, F., Gao, Y., Ding, J., & Chen, Q., 2017. Is the positivity of estrogen receptor or progesterone receptor different between type 1 and type 2 endometrial cancer? Oncotarget, 8(1), 506-511. https://doi.org/10.18632/oncotarget.13471.

Slomovitz, B.M., Jiang, Y., Yates, M.S., Soliman, P.T., Johnston, T., Nowakowski, M., Levenback, C., Zhang, Q., Ring, K., Munsell, M.F., Gershenson, D.M., Lu, K.H., Coleman, R.L., 2015. Phase II study of everolimus and letrozole in patients with recurrent endometrial carcinoma. J Clin Oncol 33 (8), 930–936. https://doi.org/10.1200/JCO.2014.58.3401.