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Case report

Aromatase inhibitor therapy in recurrent, estrogen-receptor positive uterine serous carcinoma: A case report

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1. Introduction

Uterine serous carcinoma (USC) is a subtype of endometrial cancer associated with poorer survival outcomes compared to the more common subtype, endometrioid endometrial carcinoma (EEC). The biologically aggressive nature of this malignancy has prompted investigation of novel treatments, particularly targeted therapies tailored to the specific gene and receptor expression profiles in individual patients. For instance, targeting tumors that overexpress HER2 with trastuzumab reduces recurrence rates and increases progression free survival in women with advanced or recurrent USC (Fader et al., 2018). Hormone receptors, namely estrogen receptors (ER) and progesterone receptors (PR), are other potential therapeutic targets in USC.

While endocrine therapy has not been evaluated in USC, it is commonly used in EEC, where over 90% of tumors express ER or PR (Shen et al., 2017). Progestin-based treatments have been adopted in advanced or recurrent endometrial carcinoma (Koh et al., 2018). Recent trials have demonstrated the efficacy of other regimens in recurrent endometrial carcinoma, including alternating megestrol acetate and tamoxifen or the combination of everolimus and letrozole (Fiorica et al., 2004; Slomovitz et al., 2015).

A substantial proportion of USC tumors also express ER and PR. An analysis of 628 USC tumor samples demonstrated ERα and PR expression in 60% and 32% of tumors respectively (Jones et al., 2015). However, studies of the genomic profiles of USC and EEC suggest that different molecular pathways are involved in the pathogenesis of these tumors (Levine and Network, 2013). These data support the hypothesis that EEC and USC are separate entities, raising the question of whether endocrine therapy can be utilized to effectively treat USC as in EEC. This case report describes the treatment of a woman with ER-positive, recurrent, metastatic USC with letrozole, an aromatase inhibitor.

2. Case report

A 61-year-old black, gravida 1 para 1 female with a BMI of 33.6 kg/m^2 underwent a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic and *para*-aortic lymphadenectomy, demonstrating stage IIIC1 USC on pathology. Her past medical history was significant for atrial fibrillation, hypertension, and depression, all well-controlled pharmacologically. Her family history was notable for pancreatic cancer in her mother. She had a 20 pack-year smoking history with cessation 2 decades prior to diagnosis. After surgery, she received 6 cycles of adjuvant carboplatin-paclitaxel chemotherapy.

The patient experienced disease-free survival for over 9 years until routine surveillance imaging revealed innumerable punctate osseous blastic lesions in the vertebral column, as well as two sub-centimeter lung nodules. These lesions were new developments, strongly suggesting metastatic disease (Fig. 1a, 1b). PET/CT showed no fluorodexyglucose (FDG)-avidity, and bone scintigraphy demonstrated no increased uptake of the radiotracer, Tc99m-methyl-diphosphonate. At this time, the patient reported a new complaint of right buttock pain that radiated down her leg and worsened with exertion. X-ray imaging of the hip showed additional blastic lesions in the right pelvis and femoral head. A biopsy of the right iliac crest confirmed the diagnosis of metastatic poorly-differentiated carcinoma, consistent with the patient's known USC. On immunohistochemical analysis, the sample stained diffusely positive for ER and negatively for HER2 (Fig. 2).

The patient began a chemotherapy regimen of intravenous carboplatin-paclitaxel every 21 days, with concurrent intravenous zoledronic acid 4 mg every 4 weeks to promote bone health. Her CA-125 level prior to chemotherapy was 14U/mL. The chemotherapy regimen was marked by significant neurological adverse effects. After two cycles, she experienced unilateral facial nerve palsy, reporting difficulty closing her left eye and smiling. MRI imaging of the brain revealed a 4x7mm focal enhancement in the left internal auditory canal, raising suspicion for a metastasis or a vestibular schwannoma. The lesion was monitored through routine imaging, and chemotherapy was continued as planned. By the time the patient completed her fourth cycle, she had developed grade 3 peripheral motor neuropathy, reporting lower extremity weakness and frequent falls. These symptoms prompted a 4-day

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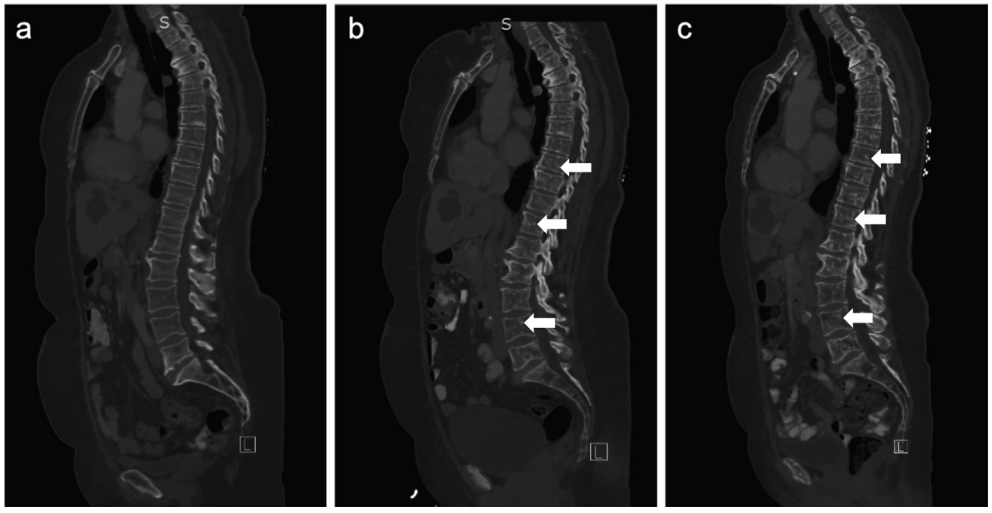

Fig. 1. (a) Sagittal CT image 12 months prior to recurrence obtained from outside medical institution, where no sclerotic lesions are visible. (b) Sagittal CT image at the time of diagnosis of recurrence, showing innumerable punctate sclerotic lesions throughout the spine. Examples of sclerotic foci are indicated with white arrows. (c) Sagittal CT image demonstrating stable disease 2 years following the initiation of letrozole therapy. Examples of sclerotic foci are indicated with white arrows.

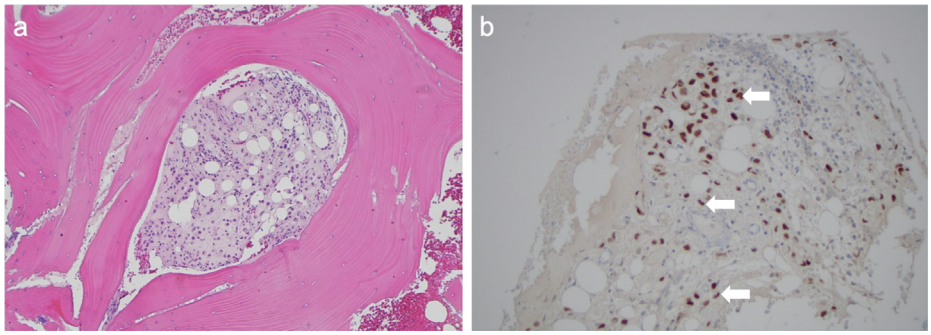

Fig. 2. (a) Hematoxylin and eosin (H&E) stain of biopsy sample obtained from the right iliac crest, demonstrating the recurrence of uterine serous carcinoma, metastatic to bone. (b) Immunohistochemical staining of the biopsy sample for ER at 200× magnification. Strong, diffuse nuclear expression of ER is exhibited in tumor cells and is indicated by white arrows.

admission, where the patient experienced an acute kidney injury in the setting of dehydration, with creatinine rising to 2.0 mg/dL from 0.8 mg/dL at baseline. She now required a walker to ambulate, and her ECOG performance status worsened to 3 from a baseline of 0. At the completion of the sixth cycle of chemotherapy, the patient's poor functional status prompted discussions of hospice care. Cytotoxic chemotherapy was discontinued, and her CA-125 level was 17U/mL. CT imaging at the completion of chemotherapy showed no significant changes.

At a follow-up appointment 12 weeks after the completion of chemotherapy, the patient's performance status had improved to an ECOG score of 1. She felt stronger, and her facial paresis had resolved completely. She began letrozole 2.5 mg daily therapy for her ER-positive disease, while continuing intravenous zoledronic acid therapy. Regarding the internal auditory canal lesion, repeat brain MRI showed no changes at 3, 9, and 15 months, and yearly thereafter. The lesion was deemed to be a likely vestibular schwannoma rather than metastatic USC.

Since the initiation of combined letrozole-zoledronic acid therapy 30 months ago, the patient has had no evidence of disease progression on CT imaging every 6 months, with the most recent scan depicted in Fig. 1c. Her neurological symptoms have improved significantly, and she continues to have stable grade 2 neuropathy, with decreased sensation at her fingertips and the soles of her feet. She often wears thin gloves to minimize the symptoms, and she has declined therapeutics or interventions to improve these symptoms. Now 73-years-old, the patient is fully ambulatory with an ECOG score of 0, and she leads an active lifestyle mostly unimpeded by her illness.

3. Discussion

Given the tumor biology of USC and the limited repertoire of available treatments, there is a critical unmet need for therapeutic options in women with advanced stage or recurrent disease. Investigators should weigh the overall clinical benefit of potential treatments, including criteria for both survival and quality of life. In this case report, carboplatin-paclitaxel chemotherapy led to significant neurological side effects with no improvement in tumor status. The patient's functional debilitation affected perceptions of disease prognosis and prompted discussions of hospice care. In contrast, the patient found letrozole therapy tolerable with minimal adverse effects. Letrozole therapy in USC has not been investigated thus far, yet it demonstrated substantial clinical benefit in this particular case. The patient has maintained an excellent quality of life while remaining progression-free for 30 months to date.

Weighing the clinical benefit of letrozole requires an understanding of its adverse effect profile. Letrozole is well-tolerated, particularly compared to chemotherapy, but patients may experience symptoms similar to those of menopause: hot flashes, night sweats, and weight gain. Arthralgias and myalgias are also occasionally reported. Letrozole may increase cholesterol levels but has no significant adverse impact on cardiovascular outcomes. In terms of bone health, estrogen suppression by letrozole may lead to the loss of bone mineral density.

In patients receiving aromatase inhibitor therapy, concurrent treatment with zoledronic acid reduces the risk of progression to osteopenia and may exhibit synergistic antitumor effects. A recent trial followed 1065 women with early-stage breast cancer, randomized to receive letrozole with or without zoledronic acid. Not only did zoledronic acid increase lumbar spine bone mineral density, but it also reduced the risk of local and distant recurrence (Coleman et al., 2013). USC shares clinical and pathological features with basal-like breast carcinomas (Levine and Network, 2013). Therefore, the observed efficacy of combined letrozole-zoledronic acid treatment in hormone-sensitive breast cancer may be applicable to USC as well. Furthermore,

preclinical studies have demonstrated independent antitumor properties of bisphosphonates, including induction of apoptosis, inhibition of invasion, and modulation of tumor-associated macrophages (Neville-Webbe et al., 2010). Zoledronic acid appears to serve two functions: preventing osteopenia and potentially enhancing the efficacy of letrozole against hormone-sensitive tumors.

This report also describes the metastasis of USC to bone. In cases of osseous metastases, treatment with osteoclast inhibitors such as zoledronic acid is particularly important to promote bone stabilization. It remains unclear whether the antitumor effects of zoledronic acid are enhanced against bone metastases.

Treatment strategies for USC are predominantly based on studies that include other endometrial cancer subtypes. USC patients are often poorly represented in such studies in comparison to the more common subtype, EEC. ER/PR-positive EEC is responsive to progestin- and aromatase inhibitor-based treatments (Fiorica et al., 2004; Koh et al., 2018; Slomovitz et al., 2015). However, the clinical significance of ER/PR expression in USC is poorly understood. In a study of 71 women with USC, ER or PR expression was associated with lower recurrence rates and longer recurrence-free and overall survival (Togami et al., 2012).

Guidelines for evaluating ER expression have not been described in USC specifically. The limited existing data suggest that a substantial portion of USC appears to express ER and may have a more indolent course than the ER-negative variant. Consistent with such observations, this report describes the relatively indolent course of metastatic, ER-positive USC in one patient. Furthermore, this report suggests that letrozole may exhibit clinical and survival benefits in patients with ER-positive USC, particularly in combination with zoledronic acid. In contrast, a recent phase II trial of everolimus and letrozole in recurrent endometrial carcinoma found that the 7 patients with serous histology did not respond to letrozole (Slomovitz et al., 2015). The ER status of the tumors was not assessed. One question arising from these divergent findings is whether the degree of ER expression impacts the efficacy of aromatase inhibitor therapy.

In summary, this report describes a case of ER-positive USC, widely metastasized to the bone, with a remarkable response to letrozole therapy. Zoledronic acid was started concurrently with chemotherapy and did not demonstrate clear clinical benefit at the time. When letrozole maintenance therapy was added to the regimen, the patient experienced symptomatic improvement and no further disease progression. These observations suggest that letrozole may have been the major driver of stable disease. This case report encourages further exploration of aromatase inhibitor therapy in ER-positive USC, as well as regular pathological testing of USC tumor samples to identify targets for therapy. The potential synergistic effects of letrozole and zoledronic acid also warrant further study. This would provide a novel option to patients in critical need of therapeutic alternatives.

4. Consent statement

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

CRediT authorship contribution statement

Omar Najjar: Writing - original draft, Project administration. **Aaron Varghese:** Writing - review & editing. **Maryam Shahi:** Visualization, Writing - review & editing. **Russell Vang:** Writing - review & editing. **Stephanie Gaillard:** Writing - review & editing. **Thomas Smith:** . **Amanda N. Fader:** Conceptualization, Supervision, Writing - review & editing.

Declaration of Competing Interest

Dr. Stephanie Gaillard reports the following disclosures outside of the submitted work: grants and personal fees from Merck, Tesaro, Pfizer, Genentech/Roche, PharmaMar; grants to institution from Abbvie, Bristol-Myers Squibb, Gradalis, Iovance Biotherapeutics, Tetralogic Pharmaceuticals; personal fees from AstraZeneca and Immunogen. Otherwise, the authors certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this manuscript.

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