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Case report

Clear cell adenocarcinoma arising from anterior abdominal wall cesarean section scar endometriosis treated with excision and the addition of Trastuzumab for adjuvant chemotherapy: A case report

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ABSTRACT

Abdominal wall endometriosis with subsequent transformation to clear cell carcinoma is quite rare. The pathogenesis and pattern of this transformation is not well known; hence evaluation and management guidelines are not well established. We highlight a case of clear cell adenocarcinoma arising from the anterior abdominal wall in a previous cesarean section scar treated with excision and the unique addition of Trastuzumab for adjuvant chemotherapy.

1. Introduction

Endometriosis, a common condition in women of reproductive age, is defined as endometrial-like tissue arising external to the uterus that often leads to chronic pelvic pain and menstrual irregularity. Endometriosis of the abdominal wall has been reported in surgical scars following cesarean section and other invasive gynecologic surgeries (Marques et al., 2017). Although endometriosis may occur in as many as 15% of women of reproductive age, its prevalence is around 0.03–0.4% of abdominal wall scars resulting from gynecologic surgery (Stevens, 2013). One percent of all endometriosis cases may progress to malignant disease, and only about 4.5% of these transformations demonstrate clear cell histology (Ferrandina et al., 2016). Due to the infrequency of clear cell carcinoma of the abdominal wall, neither treatments nor outcomes are well established. Reported cases have received treatment with a combination of surgical excision, radiotherapy, and chemotherapy. Prognosis however remains poor, with a median survival of approximately 30 months (Marques et al., 2017; Ferrandina et al., 2016). To add to the growing literature regarding this uncommon diagnosis, we report a case of clear cell carcinoma arising from an endometriosis focus located within a cesarean section scar and the use of Trastuzumab as part of the adjuvant chemotherapy regimen after surgical excision.

2. Case report

A 54-year-old G2P2002 patient presented to the gynecology service at our institution with worsening burning discomfort involving the right lower abdomen. She had a long history of biopsy proven endometriosis which was managed with oral contraceptive pills (OCPs). She underwent a low transverse cesarean section via Pfannenstiel incision in 1998. And 5 years later, she complained of pain and swelling of her right lower abdominal wall. A firm nodule was appreciated and subsequently biopsied. The pathology at that time was consistent with endometriosis. She then continued her OCPs. In October 2020 she reported increased burning discomfort to the right lower abdomen. Abdominal examination was noteworthy for a palpable tender mass in the right lower quadrant just superior to the lateral aspect of her previous Pfannenstiel incision. There was also an enlarged, right inguinal femoral lymph node. Pelvic examination was otherwise within normal limits.

Evaluation with Magnetic Resonance Imaging (MRI) of the pelvis revealed a 72 × 41 × 62 mm right lower abdominal wall mass with 2 satellite lesions measuring 24 × 16 × 20 and 16 × 14 × 9 mm respectively in the right inguinal region (Fig. 1a, b, c) representing lymphadenopathy. No pelvic or adnexal masses were identified, and the uterus was heterogenous measuring 132 × 56 × 67 mm. An ultrasound-guided biopsy of the mass was then performed (Fig. 1d).

Histopathology revealed high grade adenocarcinoma with clear cell

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features; and associated benign epithelium and stroma suggestive of endometriosis (Fig. 2). Immunostains showed that the carcinoma was positive for CK7, PAX-8 and napsin A, and negative for CK20, CDX-2, TTF-1, estrogen receptor (ER) and GATA3. The benign foci suggestive of endometriosis was positive for ER (stroma and epithelium), WT-1 (stroma) and CD10 (stroma, focal).

After review with the gynecologic oncology and medical oncology teams; complete staging studies with Computer Tomography (CT) of the chest, abdomen and pelvis were performed. Her chest CT scan showed no identifiable abnormality. The abdominal CT scan however demonstrated the abdominal wall mass along the right rectus musculature and associated right inguinal, right external iliac lymphadenopathy concerning for metastatic disease. Laboratory tests revealed CA125 of 45 U/mL.

The patient subsequently underwent excision of the abdominal wall mass (Fig. 3), right inguino-femoral lymph node dissection, total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and periaortic lymph node dissection, omentectomy and primary complex closure of the abdominal defect with mesh placement.

The final pathology report of the excised abdominal wall mass was consistent with clear cell carcinoma with negative margins. There were two out of four positive right inguinal nodes; one positive inferior epigastric node; two out five positive right obturator nodes; and five negative right external iliac nodes. The uterus, cervix, bilateral Fallopian tubes, and ovaries had benign findings. The patient recovered well from her procedure and started adjuvant chemotherapy with weekly Carboplatin AUC2 and Paclitaxel 80 mg/m2. Biomarker findings showed microsatellite status stability and Tumor Mutational Burden of 3 mutations per megabase (Muts/Mb). Immunostaining revealed overexpression of human epidermal growth factor receptor 2 (HER2)/neu) in the tumor. The Her2/neu-positive status of the patient was determined using formalin-fixed, paraffin embedded section of tumor tissue and was tested against Her2/neu antibody. The patient's Her2/neu histochemical score was 3 + based on the American Society of Clinical Oncology/College of American Pathologist guideline recommendations (2018). The staining pattern identified was circumferential membrane staining that was complete, intense, and within greater than 10% of the tumor cells.

Trastuzumab was added to her chemotherapy regimen starting at a loading dose of 8 mg/Kg then 6 mg/kg every 3 weeks. The patient completed a further six planned treatment cycles of chemotherapy. A follow up CT scan nine months post-surgery revealed positive clinical response to therapy with no new sites of disease identified within the chest, abdomen, or pelvis. The patient remains under active surveillance with the medical and gynecologic oncology teams.

3. Discussion

Approximately 18 cases of clear cell carcinoma of the abdominal wall arising from scar endometriosis have been reported to date. Endometrioid and serous carcinoma have also been described in the literature (Wei and Huang, 2017). Most cases have been associated with a pre-existing history of endometriosis, and all cases have been associated with prior abdominal surgery, mainly cesarean section, or resection of endometriosis (Stevens, 2013). Prior studies demonstrated a delay greater than 20 years between surgery and the development of abdominal wall cancer. The Interval between cesarean section as the primary surgery to the diagnosis of clear cell carcinoma varies from approximately 9 to 30 years, with a mean of 17.9 years (Wei and Huang, 2017). Our patient was diagnosed with clear cell carcinoma 23 years after her cesarean section but had her abdominal wall mass biopsied with the pathology showing scar endometriosis 17 years prior. In one of the largest reviews, wide tumor resection with hysterectomy and bilateral salpingo-oophorectomy, as was performed in our case, was associated with the highest chance of survival with no evidence of residual disease (Ferrandina et al., 2016).

Reported abdominal wall masses range in dimensions from 2.5 to 22 cm, with a median diameter of 9 cm. Cases that have reported better outcomes had masses ranging between 4 and 9 cm (Ferrandina et al., 2016; Wei and Huang, 2017). A prosthetic mesh for abdominal wall closure, as was employed in our patient is often needed owing to the large defect left after resecting the mass and ensuring clean margins.

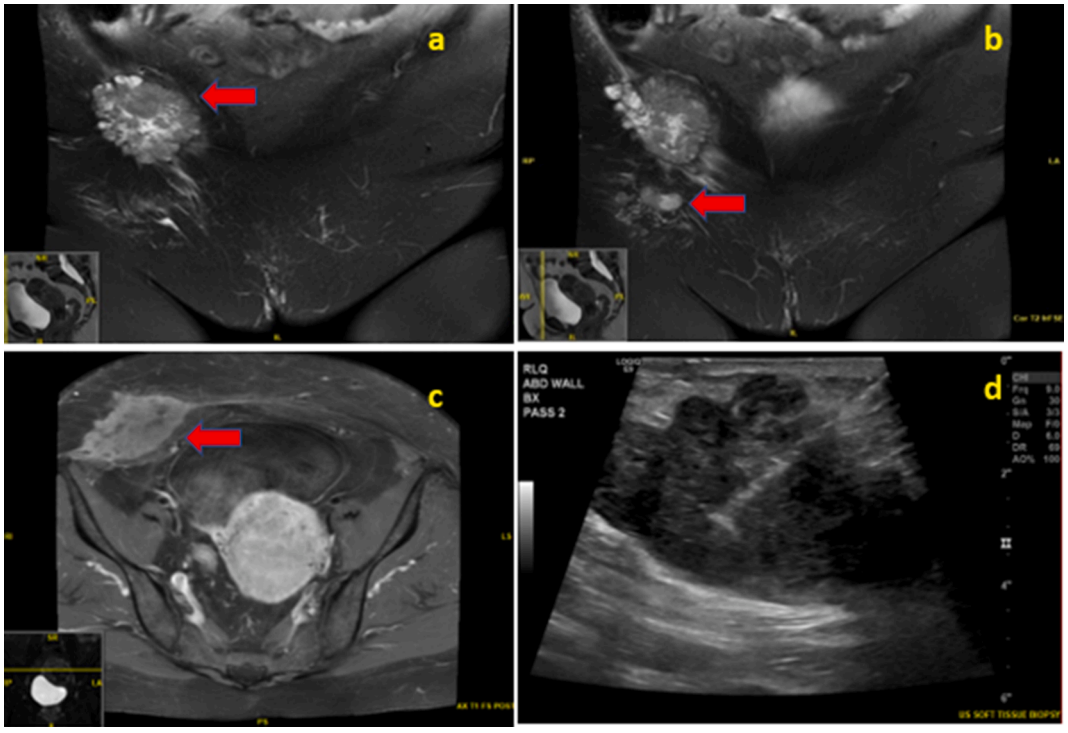

Fig. 1. a. MRI Coronal view of mass in anterior abdominal wall **b.** Satellite lesion on MRI **c**. Transverse MRI view of mass in the anterior abdominal wall. **d**. Ultrasound guided biopsy of the mass.

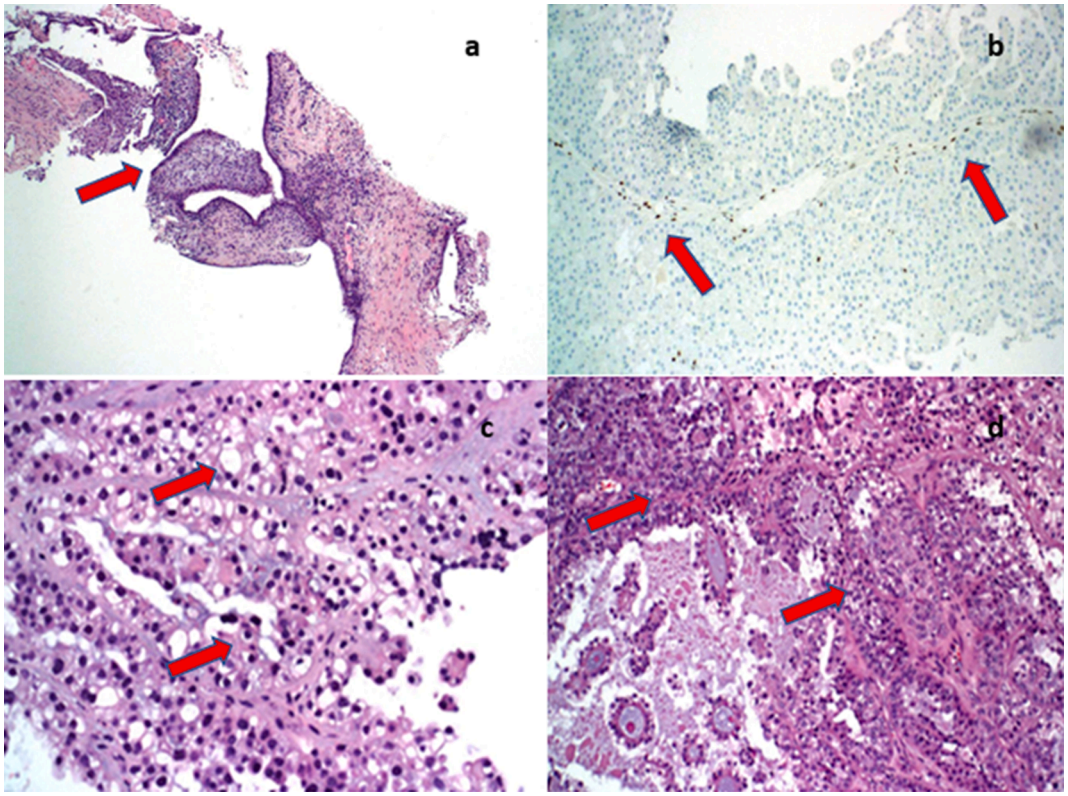

Fig. 2. **a**. Areas of endometriosis showing endometrial glands and stroma **b**. ER-positive staining **c**. Neoplastic cells with large clear cytoplasm **d**. Malignant cells with high-grade nuclear atypia.

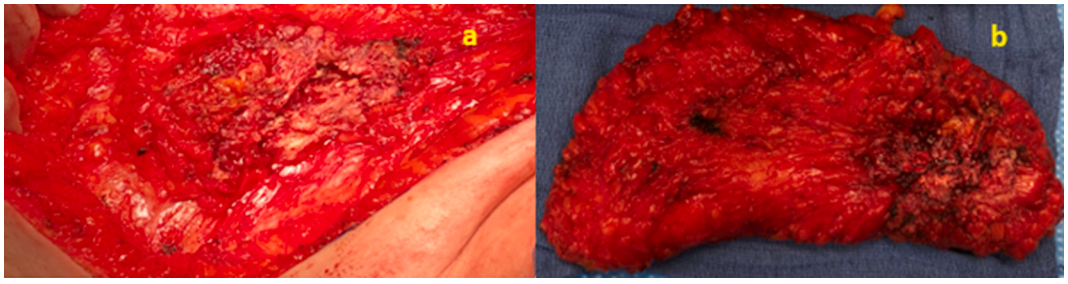

Fig. 3. **a**. In situ anterior abdominal wall mass at time of surgery **b.** Resected mass (measuring 9.0 × 8.0 × 3.0 cm) with negative margins on pathology.

Mesh overlay however, depends on the size and location of the defect.

While there are no current established standards or protocols for the treatment of clear cell carcinoma arising from abdominal wall endometriosis, surgery followed by adjuvant chemotherapy or radiotherapy has shown benefits in local control and metastatic disease (Marques et al., 2017; Giannella et al., 2020). As utilized in this case, Carboplatin plus paclitaxel, is the most recommended adjuvant chemotherapy regimen for this diagnosis. Our patient received weekly chemotherapy. The ICON 8 trial provided evidence that weekly dose-dense chemotherapy can be delivered successfully as first-line treatment for epithelial ovarian cancer but did not significantly improve progression-free survival compared to 3-weekly chemotherapy; and so is not the current standard of care (Clamp et al., 2019). While the superiority of weekly chemotherapy schedules has not been confirmed at our institution for selected patients, we do administer weekly paclitaxel-carboplatin. Data from the European MITO-7 trial showed no difference in efficacy between patients treated with weekly versus those treated with 3-weekly chemotherapeutic regimens for epithelial ovarian cancer; however, patients who received weekly chemotherapy experienced less toxicity and had superior quality of life during treatment (Pignata et al., 2014). The most recent study by Safra et al added data to the ongoing discussion and suggested that weekly paclitaxel carboplatin regimen is as active and sometimes better tolerated than the standard 3 -weekly regimen (Safra et al., 2021). For our patient with this rare and often aggressive form of malignancy it was a shared decision-making process. After presenting all the available evidence, she opted to be treated with the weekly chemotherapy regimen.

We additionally performed HER-2/neu testing on the resected mass and as such was able to add trastuzumab to the patient's treatment regimen once the tumor was found to be Her2/neu positive. Our patient's Her2/neu histochemical score was 3 +. Results for Her2/neu testing are reported on a scale of 0–3. Cases that are 0 or 1 + are considered negative for Her2 expression. Cases that are 3 + are considered positive. If the scoring is 2+ (defined as incomplete/weak staining in >10% of tumor cells or complete/intense staining in < 10% of tumor cells), the tumor is then tested using in situ hybridization (Fader et al., 2018). Her2/neu provides signalling for cancer growth and its overexpression contributes to oncogenic transformation, tumorigenesis, and metastatic potential (Fader et al., 2018; Santin et al., 2008). Trastuzumab is a humanized monoclonal antibody which binds to the

extracellular domain of the Her2/neu receptor (Thouvenin, 2021).

Clinical studies to evaluate the combination of trastuzumab and chemotherapy have relied on the premise that a synergistic effect leads to enhanced antitumor activity and subsequent higher response rate than when the agents are used separately (Fader et al., 2018; Thouvenin, 2021; Jewell et al., 2006). Approximately one-third of serous endometrial carcinomas are HER2/neu positive (by either immunohistochemistry, or FISH, or both) and a recent randomized phase 2 trial showed that the supplemental addition of Trastuzumab to carboplatin-paclitaxel was found to be well tolerated and improved progression-free survival in Her2/neu positive uterine serous carcinomas (Fader et al., 2018). Similarly, targeted immunotherapy using trastuzumab in addition to conventional chemotherapy against high grade epithelial ovarian cancer that overexpressed Her2/neu, have been associated with complete response in one cohort of patients (Guastalla et al., 2007). In the Gynecologic Oncology Group studies, however, the use of trastuzumab alone in women with advance or refractory endometrial carcinoma, ovarian cancer or primary peritoneal carcinoma showed a low response rate (Bookman et al., 2003; Fleming et al., 2010). As a chemotherapeutic adjunct, trastuzumab addition to carboplatin-paclitaxel for women with clear cell endometrial cancer arising from abdominal wall scar endometriosis and overexpressing Her2/neu may confer benefit as was seen in this case. Despite the presence of metastatic disease at the time of diagnosis, follow-up six months post treatment demonstrated no new signs of disease.

4. Conclusion

Our patient exhibited good clinical response with the addition of trastuzumab to her chemotherapy treatment. Whilst she is still under active clinical surveillance, this case highlights the fact that that trastuzumab may be a useful adjuvant to carboplatin/paclitaxel chemotherapy in patients with clear cell carcinoma arising from an endometriotic foci that overexpress HER-2/neu.

Informed Consent Statement

Written Informed consent was obtained from the patient for publication of this case report as well as the 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

Gregory K. Lewis: Conceptualization, Writing – original draft. **Shilpa N. Gajarawala:** Writing – review & editing. **Kyle E. Robinson:** Writing – review & editing. **Anita H. Chen:** Supervision, Writing – review & editing. **Matthew W. Robertson:** 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.

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