Gynecologic Oncology Reports 52 (2024) 101371

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

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

Metastatic squamous cell carcinoma arising from mature teratoma of the ovary: Description of multi-modality treatment including incorporation of adjuvant immunotherapy and maintenance PARP inhibitor therapy

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1. Introduction

Mature cystic teratomas (MCTs) are relatively common ovarian germ cell tumors that occur in 1.2–14.2 patients per 100,000 per year and are largely considered to be benign, although 0.17–2 % of MCTs demonstrate malignant transformation (Hackethal et al., 2008). About 80 % of those are characterized as squamous cell carcinoma (SCC) arising from the ectoderm (Gadducci et al., 2019). While International Federation of Gynecology and Obstetrician (FIGO) staging correlates with prognosis in the cases reported, a difference has been described between stage I and more advanced including stage II, III, and IV, with only small numbers of reported cases in the stage IV category (Hackethal et al., 2008; Chen et al., 2008). There is a dearth of information regarding optimal approach and therapy options for patients with SCC arising from MCT, particularly at more advanced stages. Previous reports demonstrate evidence for survival benefit with cytoreductive surgery in combination with carboplatin and paclitaxel (Hackethal et al., 2008). Additionally, recent case reports describe the use of immunotherapy and other targeted therapies with variable efficacy (Wu et al., 2021) (Martel et al., 2023) (Tamura et al., 2023).

Here we add to the existing literature with a report describing the use of multimodality therapy in the treatment of a SCC arising within MCT, in order to further expand options for fertility sparing, timing of treatment, and maintenance therapy, in the setting of advanced disease.

2. Case Report

A 23-year-old gravida zero female presented to Urgent Care with several months of chronic fever, intermittent night sweats, presyncope, sensitivity to cold, and fatigue. During the time leading up to presentation, she had intermittent pain with urination and with bowel movements, as well as a 10–15 lb weight loss. Of note, prior testing had been performed which demonstrated elevated thyroid peroxidase antibodies with normal thyroid function testing, and leukocytosis. On presentation she was noted to be tachycardic with heart rate in the 140′s and had alterations in her cell counts with a white blood cell count of 25.6 K/mcL, platelet count of 519 K/mcL, and a hemoglobin of 8.8 g/dL. Lactic acid was normal at 1.3 mmol/L. Computed tomography (CT) imaging of the abdomen/pelvis was performed, revealing a 11.1 x 8.8 x 11.5 cm pelvic mass anterior to the uterine fundus with abundant fat and scattered calcifications in addition to low attenuation zones and solid-appearing features. A large posterior cul-de-sac mass of 5.1 x 4.6 cm was identified between the posterior uterine margin and the anterior margin of the rectum. There was an additional 6.7 x 5.9 cm mass located in the right adrenal gland and a 3.1 cm solid lesion in the right hepatic lobe (Fig. 1). Pelvic ultrasound demonstrated bilateral teratomas anterior to the uterus; on the right measuring 6.9 x 5.1 x 10 cm and on the left measuring 9.4 x 8.7 x 12.1 cm. Imaging of the chest was negative for metastatic disease. Pertinent tumor markers were assessed – CA 19–9 < 2.06 U/mL, CA-125 89.2 U/mL (0.0–35.0 U/mL), Alpha-fetoprotein Tumor marker < 2.00 ng/mL, Beta-hCG Quant Tumor Marker 1 IU/L (0–5 IU/L), and Lactate Dehydrogenase 216 Units/L (120–246 Units/L). She was admitted to the hospital for additional evaluation, and underwent biopsy of the hepatic mass. Pathology showed p16 negative SCC, with PD-L1 TPS of 25 %. Pap cytology testing was performed, with negative/benign results and with no lesions on examination. It was determined that this most likely represented malignant transformation of mature teratoma of the ovary, with metastasis of the squamous cell carcinoma/malignant component. Multidisciplinary counseling and treatment planning were performed with Medical Oncology, Surgical Oncology, and Gynecologic Oncology. Fertility preservation was discussed and due to metastatic disease already present, a fertility sparing approach to surgery if possible was offered. Preoperative oocyte retrieval was not possible due to bilateral involvement of the ovaries.

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https://doi.org/10.1016/j.gore.2024.101371
Received 16 January 2024; Received in revised form 7 March 2024; Accepted 17 March 2024
Available online 19 March 2024

She elected to move forward with surgical management, and three weeks after diagnosis, underwent aggressive surgical debulking with exploratory laparotomy, omentectomy, left salpingo-oophorectomy, right ovarian cystectomy, resection of rectovaginal septum mass, partial rectosigmoid colon resection with end-to-end anastomosis, right adrenalectomy, and partial hepatic resection. A grossly uninvolved portion of the right ovary, the right tube, and the uterus were maintained, for consideration of fertility preservation. At the close of the procedure there was no visible or palpable residual disease. Postoperatively she initially recovered well; however, on postoperative day 6 became febrile and was found to have worsening leukocytosis. She was started on broad spectrum antibiotics for concern of infection, and CT imaging revealed a 5.5 x 4.8 x 4.5 cm mass within segment 7 of the liver with a stable cystic component adjacent to the right adrenalectomy site. There was concern for postoperative abscess, but on review of prior imaging there was also concern that this represented a site of residual disease within the hepatic parenchyma that had previously been obscured by the adjacent adrenal mass. A biopsy of the lesion was obtained and consistent with SCC (Fig. 3a).

Final surgical pathology demonstrated MCT in the right ovary, with malignant transformation to SCC (Fig. 2) with metastatic SCC to the left ovary, liver, right adrenal gland, bladder/pelvic peritoneum, uterine serosa (superficial implants), and rectovaginal septum.

Final diagnosis was stage IVB SCC of the ovary arising from malignant transformation of a MCT. Next generation sequencing (Foundation One CDx) revealed high tumor mutational (TMB) with 16 mut/Mb, microsatellite stable, homologous recombination deficiency (HRD) positive (loss of heterozygosity/LOH score 34.5 %) disease with mutations in PIK3CA, STK11, TP53, CDKN2A, NLL2, NFE2L2, and TERT promoter. Subsequent germline testing was negative (with variants of uncertain significance/VUS identified in CTNNA1 and NPAT).

The case was discussed at the institutional multidisciplinary tumor board. Multi-agent therapy was recommended, but as chemotherapy needed to be delayed for reasonable postoperative healing, it was decided to initiate earlier adjuvant treatment with pembrolizumab at two weeks after surgery. During this time, she continued to have intermittent fevers and night sweats; evaluation for infection was negative and thus these symptoms were attributed to residual tumor activity in the hepatic mass. Five days after starting pembrolizumab, her fevers and night sweats completely subsided. Early CT imaging performed for mild rectal bleeding three weeks after the start of pembrolizumab showed increased heterogenous hypo-enhancement in the hepatic parenchyma surrounding the residual hepatic mass (Fig. 3b), potentially indicating early response to immunotherapy.

At 5 weeks postoperatively, carboplatin and paclitaxel were initiated

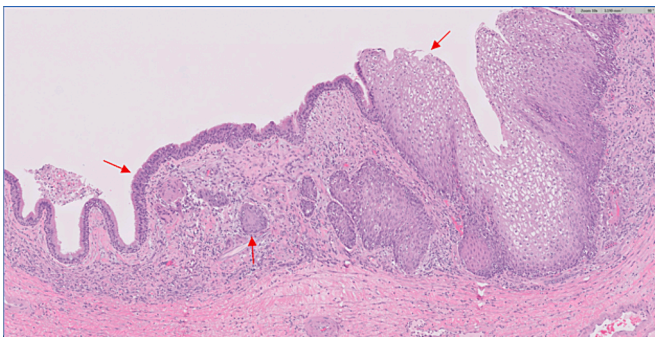

Fig. 2. Ovarian teratoma with squamous cell carcinoma (hematoxylin and eosin stain, 100X magnification). The tumor cyst lining is composed of multiple mature tissue types, including respiratory epithelium (left arrow) and non-keratinizing squamous mucosa (right arrow). Early invasive squamous cell carcinoma (center arrow) is present.

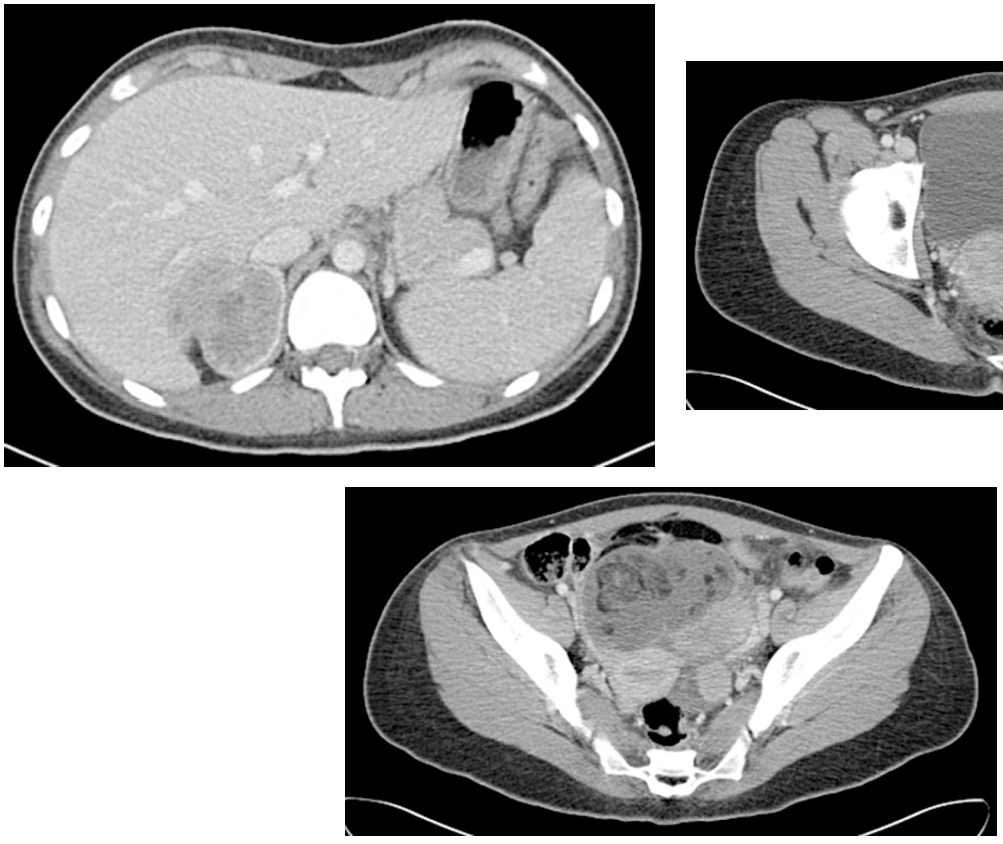

Fig. 1. Axial view of Computed Tomography imaging of abdomen and pelvis upon presentation. (a) Right adrenal gland mass. (b) Rectovaginal septum mass. (c) Uterus and bilateral ovary metastatic involvement.

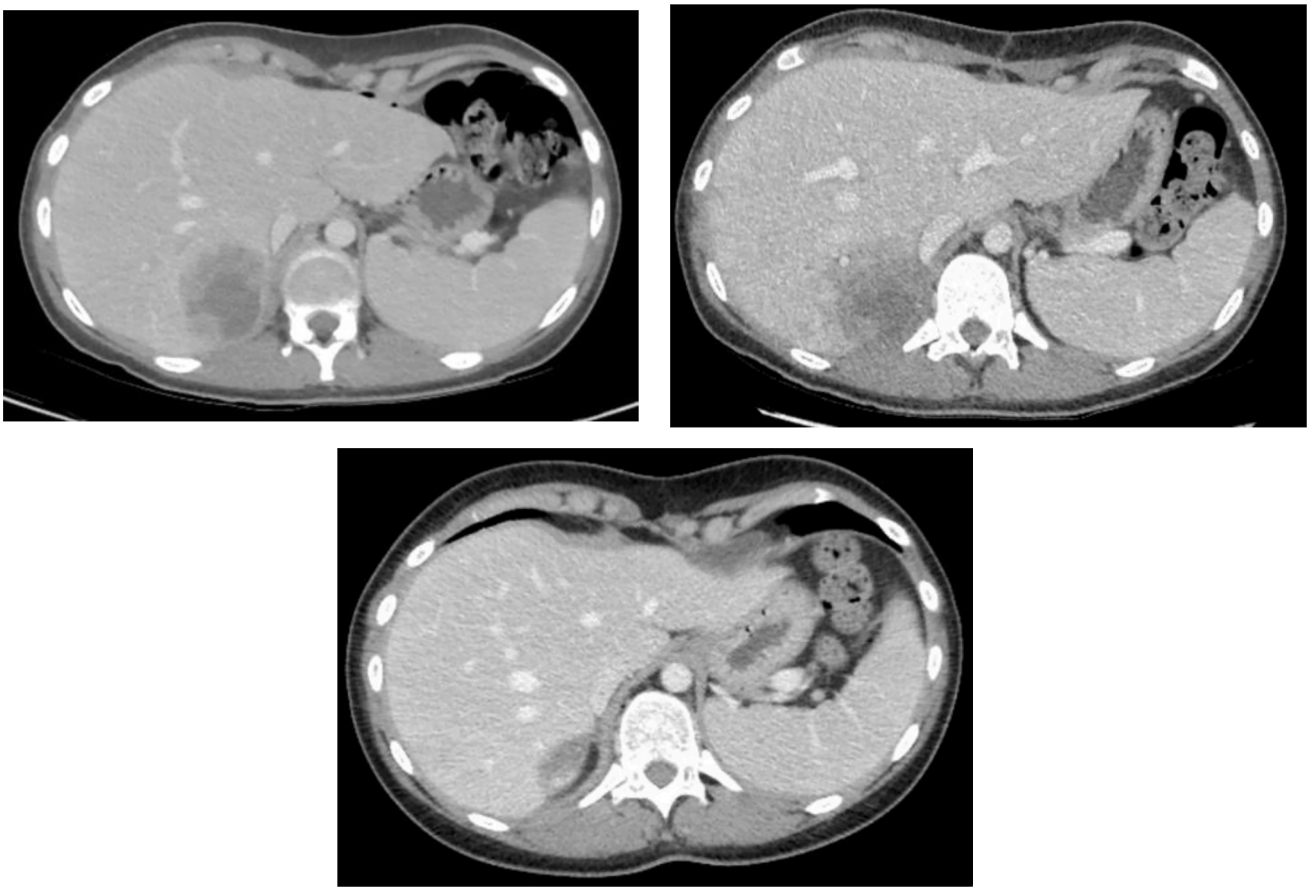

Fig. 3. Computed tomography of the residual hepatic mass during treatment. (a) Post-operative site of residual disease. (b) Early CT three weeks after start of pembrolizumab. (c) CT one month after the conclusion of chemotherapy regimen.

in combination with pembrolizumab, with interval imaging after 3 cycles and then 6 cycles of systemic therapy. There was no evidence of new disease, and the liver lesion had decreased in size from 5.8 x 4.4 x 4.8 cm to 2.9 x 1 cm (Fig. 3c).

Options for the residual liver lesion were discussed, including surgical resection, stereotactic body radiation therapy (SBRT), and proton SBRT. She elected to proceed with proton SBRT for the residual mass, 11 Gy over 5 fractions, and continued pembrolizumab during treatment without immunotherapy-mediated side effects. CA-125 normalized over the course of treatment. At the close of active treatment with radiation therapy, Signatera ctDNA was performed which was negative, with 0 mean ctDNA molecules/mL plasma detected.

Overall, she tolerated treatment well but about one month after administration of pembrolizumab, demonstrated signs of immune checkpoint inhibitor induced thyroiditis with asymptomatic hyperthyroidism. At the time, no clinical interventions were performed as she was asymptomatic. Two months after initial hyperthyroidism, she was noted to have a brief period of euthyroid testing and then demonstrated signs of hypothyroidism. Levothyroxine supplementation was initiated and continues at this time.

Due to her HRD positive disease, olaparib was added to pembrolizumab for ongoing maintenance therapy. At present, she reports excellent quality of life with minimal side effects from therapy, and at this time has been on combination maintenance therapy with olaparib and pembrolizumab for 7 months. Signatera ctDNA testing continues to be negative, and imaging demonstrates post-treatment change and no evidence of recurrent disease.

3. Discussion

For rare malignancies, there is generally a paucity of data to guide the best approach to treatment. Individualized treatment that accounts for the goals and desires of the patient, as well as the specific variables of their disease, is paramount. It is also important to consider what may be learned from other more commonly treated malignancies.

Mature teratomas are germ cell tumors that occur in approximately 10–20 % of females throughout their lifetime. While they uncommonly harbor malignant transformation, SCC of the ovary is the most prevalent malignant conversion with a mean age of 53.5 years at diagnosis (Li et al., 2019). Upon diagnosis, most cases present as stage I (50.0 %) with fewer cases in stage II (18.8 %), stage III (26.8 %), and stage IV (4.4 %). More advanced stages are associated with worse prognosis with overall 5-year survival described in one of the larger case series as 85.8, 39.1, 26.2, and 0 % for stage I, II, III, and IV, respectively (Li et al., 2019).

The combination of carboplatin and paclitaxel has been a foundational regimen for the treatment of ovarian carcinoma and other gynecologic cancers for some time, with previous reports indicating efficacy for SCC arising from MCT (Gadducci et al., 2019) (Chiang et al., 2011). More recently, immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment by enhancing the ability of a patient's T-cells to target tumor cells. PD-L1 is a ligand expressed by tumor cells to evade the immune response by binding to the checkpoint protein, programmed cell death protein 1 (PD-1). Anti PD-1 receptor monoclonal antibodies such as pembrolizumab (Keytruda®) prevent activation of PD-L1 and PD-L2 in T-cells, preventing T-cell death. Tumor tissue PD-L1 expression and tumor mutational burden correlates with ICI treatment response in solid tumors (Bai et al., 2020) (Rizvi et al., 2015) (Marabelle et al., 2020). Poly ADP-ribose polymerase (PARP) inhibitors are another

biomarker-driven therapy increasingly utilized for the treatment of gynecologic cancers, effective in increasing DNA damage and resultant cell death. PARP inhibitors are particularly beneficial when homologous recombination deficiency (HRD) is present in cancer cells, resulting in synthetic lethality and selective cell death (Liu et al., 2014; Swisher et al., 2017). PARP inhibitors can lead to higher mutational burden, increased neoantigen formation, and activation of cytokine expression in tumor cells through release of damaged DNA into the cytosol, which may contribute to a synergistic effect with immunotherapy. Tumor mutational burden (TMB) is associated with sensitivity to pembrolizumab monotherapy in solid tumors with high burden defined as a TMB of 10 mutations/megabase (Muts/Mb) (Marabelle et al., 2020). SCC arising from mature teratomas do tend to demonstrate high mutational burden with one study reporting an average of 10.2 Mut/Mb (Cooke et al., 2017). In genomic profiling, TP53 was the most common mutation (80 %) and has been associated with good prognostic factors. Other frequently altered genes include PIK3CA (52 %) and CDKN2A (44 %), but these did not seem to correlate with prognosis (Cooke et al., 2017). These latter mutations may predict sensitivity to therapies such as those targeting PI3K, AKT, or mTOR.

There are two published case reports of MCT with SCC transformation treated with pembrolizumab (Wu et al., 2021) (Martel et al., 2023). In one case, a patient with SCC and TPS of 40 % progressed with first line carboplatin, paclitaxel and pembrolizumab treatment (Martel et al., 2023). In the other, a patient with a tumor PD-L1 expression of 50–60 % showed response to pembrolizumab as a monotherapy after progressing on carboplatin, paclitaxel, and bevacizumab (Wu et al., 2021), although that regimen has been described as effective in other cases (Fukase et al., 2020) (Tamura et al., 2023), with one of those reports also describing the use of olaparib together with bevacizumab maintenance therapy for a patient with an HRD positive tumor (Tamura et al., 2023).

In this case, we considered the incorporation of immunotherapy and targeted agents into the treatment of other SCC of gynecologic origin, notably the KEYNOTE 826 trial which demonstrated both a progression-free and overall survival benefit with the addition of pembrolizumab to platinum-based chemotherapy, with or without bevacizumab, for PD-L1 positive cervical carcinoma (Colombo et al., 2021). We also considered the significant benefit, in both progression-free and overall survival, seen with PARP inhibitor maintenance in the PAOLA-1 trial for patients with HRD even without BRCA mutations, in ovarian carcinoma (Ray-Coquard et al., 2023), and did consider the addition of bevacizumab. Ultimately, in the interest of not compounding side effects from multiple agents without clear benefit, and with the prognostic indicators of PDL1 and HRD status in favor of pembrolizumab and olaparib, bevacizumab was not added to her regimen. While not available at the time of our patient's counseling regarding treatment options, the recent favorable results reported for the DUO-E trial in endometrial carcinoma add further support to the idea of combining PARP inhibitors with pembrolizumab for maintenance therapy (Westin et al., 2023:). Timing of immunotherapy will be of ongoing interest to explore in terms of maximum benefit - there are data in mouse models and in patients undergoing surgery for melanoma, that suggest immunotherapy in the neoadjuvant setting (or with active cancer present) may be more effective due to expansion of existing antitumor T-cells both in the tumor and in circulation, before surgical resection (Liu et al., 2016; Patel et al., 2023).

This is the first demonstrated use of first line pembrolizumab and maintenance olaparib for SCC from MCT in combination with surgery, cytotoxic chemotherapy, and proton radiotherapy. Fertility sparing is an important aspect of gynecologic cancer treatment to consider, recognizing the importance of maximizing oncologic outcomes while also acknowledging patient goals. Successful pregnancies have been described following fertility sparing staging in early-stage disease, as well as conservative surgical management in other cases, but there are minimal data regarding this approach and outcomes (Gadducci et al., 2019). In this case, careful counseling was performed regarding the lack of data regarding this approach but given extra-ovarian disease and need for multimodality therapy in addition to surgery, a fertility sparing approach was utilized. She has been referred to Reproductive Endocrinology and Infertility.

In conclusion, malignant transformation of MCT to SCC is a rare, often devastating disease when diagnosed at presentation with extra-ovarian metastasis. However, the continued utilization of aggressive cytoreductive surgery, the incorporation of new systemic therapy options, and potentially the alteration of therapy timing and use of maintenance therapy, will hopefully change that. Our patient had an excellent response to complete peritoneal cavity cytoreductive surgery, followed by combination therapy with cytotoxic chemotherapy and immunotherapy (with first cycle of immunotherapy alone), proton radiotherapy, and now maintenance therapy with olaparib and pembrolizumab. Next generation sequencing of her tumor, ongoing discussion regarding her goals of care, and a multidisciplinary and multimodality approach to treatment were key. Of note, she reports excellent quality of life and has returned fully to her pre-treatment work and activities.

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.

Ms. Peluso, Dr. Edwards, and Dr. Janco all contributed to the conceptualization of the report.

Ms. Peluso formulated the initial draft; Dr. Edwards and Dr. Janco contributed to editing and review.

Ms. Peluso and Dr. Janco were responsible for obtaining clinical data and resources/literature review.

Dr. Janco has participated once on an advisory board for AstraZeneca.

Aside from that, the authors have no conflicts of interest to declare.

CRediT authorship contribution statement

Esther Peluso: Writing – review & editing, Writing – original draft, Resources, Data curation, Conceptualization. **Wesleigh Fowler Edwards:** Writing – review & editing, Conceptualization. **Jo Marie Tran Janco:** Writing – review & editing, Resources, Data curation, 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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