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Case report

High-dose chemotherapy and stem-cell rescue for salvage therapy for relapsed malignant mixed ovarian germ cell tumor: A case report

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ABSTRACT

Background: Malignant ovarian germ cell tumors are rare, and often treatable with surgery and chemotherapy. Few data are available for treatment of platinum-resistant tumors.
Case: A 31 year old gravida 0 with a 20 cm pelvic mass was found to have a malignant ovarian germ cell tumor after she underwent debulking surgery. She initially responded to chemotherapy; however her AFP began to rise before all cycles were completed. She underwent additional debulking surgery that was again suboptimal. She was then referred for salvage therapy with high-dose chemotherapy with stem cell transplant, which was successful and she has had no evidence of disease for over two years.
Conclusion: High-dose chemotherapy with stem cell transplant is a viable salvage therapy for patients with platinum-resistant germ cell tumors.

1. Background

Malignant ovarian germ cell tumors (MOGCTs) are rare, constituting 2–3% of all ovarian malignancies and generally occurring in children and women of reproductive age (Brown et al., 2014). The initial management and staging of MOGCTs is surgical. In the majority of cases, the tumor is confined to one ovary, and fertility can be spared. However, when patients present with advanced disease, cytoreductive surgery with the goal of optimal or complete gross resection is advised. Surgery is followed by chemotherapy, typically bleomycin, etoposide, and cisplatin (BEP). This regimen was originally extrapolated from chemotherapy regimens used for testicular cancer(Gershenson, 2007).

While the combination of surgery and chemotherapy is sufficient for most patients with MOGCTs, a minority of patients will have persistent or recurrent disease (Gershenson, 2007). If recurrence is within 4–6 weeks of therapy, patients are considered to have platinum-resistant disease (Brown et al., 2014). In these patients, data regarding further treatment are lacking. In male patients with platinum-resistant testicular germ cell tumors, high-dose chemotherapy with stem cell transplant has been used successfully as salvage therapy (Einhorn et al., 2007a). Here, we report a case of a woman with platinum-resistant metastatic yolk sac tumor that responded to salvage therapy with high-dose chemotherapy and stem cell rescue.

2. Case

The patient is a 31 year old gravida 0 who presented to an outside emergency department reporting a sudden onset of abdominal distention and pain, as well as an unintentional 50-lb weight loss over four months. She reported no significant past medical or surgical history. Her only medication usage consisted of combined oral contraceptive pills. She had no family history of gynecologic or other malignancies. A computed tomography (CT) scan of the abdomen and pelvis revealed a complex 18 cm mass originating from the right ovary, with evidence of peritoneal and diaphragmatic metastases, as well as large volume ascites and lymphadenopathy. She was promptly referred to gynecologic oncology for further evaluation.

On presentation to the gynecologic oncology office, she reported no new symptoms. Her physical exam was remarkable for a distended and tense abdomen with palpable upper abdominal nodularity. A pelvic exam revealed a firm, fixed pelvic mass with associated rectal compression. Tumor marker evaluation showed CA-125447.8, Beta hCG < 2, CEA < 0.5, CA19–9 7.43. Based on physical exam and imaging, it was recommended that the patient undergo surgery for presumed gynecologic malignancy. In addition to routine pre-operative counseling, she was also specifically counseled on the possibility that the tumor may be unresectable and that complete resection may result in inability to preserve her future fertility. The patient agreed to

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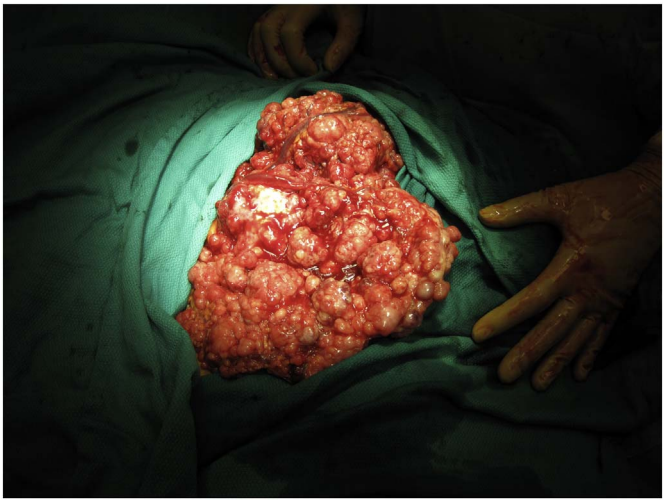

Fig. 1. Intra-operative picture showing patient's large omental cake at the time of initial tumor reductive surgery.

proceed with surgery.

The patient underwent an exploratory laparotomy, evacuation of ascites, radical hysterectomy, bilateral salpingo-oophorectomy, and radical debulking, which included omentectomy, resection of several large peritoneal carcinomatosis implants, and biopsies. She was noted to have 4 l of bloody ascites, a 20 cm cystic pelvic mass, extensive pelvic and abdominal carcinomatosis, multiple tumor nodules studding the bowels, intraparenchymal liver lesions, and a large omental cake (Fig. 1). Debulking was suboptimal.

Microscopic evaluation of the mass showed an epithelioid tumor with predominantly endometrioid glandular pattern showing elongated tubular glands and moderate to severe nuclear atypia in a loose fibromyxoid stroma. Positive staining for SALL4, AFP, and Glyp-3 plus negative Oct-4 allowed for a specific diagnosis of pure ovarian yolk sac tumor of the endometrioid glandular type (Fig. 2). Of note, this tumor aberrantly expressed other endodermal lineage markers (TTF-1 and CDX-2), which initially complicated the differential diagnosis and was included in a series of such tumors previously reported by two of the authors (HS and RR).(Shojaei et al., 2016).

AFP was checked after the procedure and noted to be 4389. She subsequently underwent adjuvant chemotherapy with BEP. After four cycles, her AFP had decreased to 13. On presentation for her sixth cycle, her AFP had increased to 25. Repeat CT showed residual disease in her liver, as well as an anterior mediastinal mass. Her AFP subsequently increased to 900. She was counseled on further chemotherapy versus further surgery for resection of the remaining disease. She proceeded with a video assisted thoracoscopic excision of the mediastinal mass and exploratory laparotomy with excision of intra-abdominal masses. This debulking was also suboptimal given the extent of her disease. The pathology of the mediastinal mass was benign, however the intra-abdominal masses were found to be malignant.

After this procedure she was referred for discussion of salvage chemotherapy. At that time, her AFP had increased to as high as 6661. She underwent two cycles of high dose chemotherapy, which consisted of 700 mg/m^2 of carboplatin and 750 mg/m^2 of etoposide daily for 3 consecutive days. This was followed by an autologous stem cell transplant. Peripheral blood cells which were collected prior to the initiation of chemotherapy were purified and then transfused back to the patient. The second cycle of chemotherapy was given after the patient had sufficient recovery of her granulocyte and platelet counts. After her second cycle, her AFP decreased to 99.5. She then received two cycles of oral etoposide 50 mg/m^2 every 21 days. Her AFP then normalized. Imaging showed resolution of her disease burden. Restaging laparotomy was performed and pathology of all suspicious areas showed necrosis and inflammation with no evidence of malignancy. Overall, the patient tolerated her therapies well, with her only persistent adverse effect being of persistent hearing loss, which has been corrected with hearing aids. At her last visit, she was 5 years out from her initial diagnosis and remains with no evidence of disease and with normal AFP levels.

3. Discussion

MOGCTs are rare. Typically, these cancers can be treated quite successfully with surgery and chemotherapy. The convention of performing cytoreductive surgery in patients with MOGCTs is derived from the treatment of epithelial ovarian cancer. There is conflicting evidence regarding the role of staging lymphadenectomy, with some sources showing evidence that lymphadenectomy is important for prognosis, and others showing that there is no additional benefit beyond helping to assign stage.(Li and Wu, 2016) In a patient such as ours (advanced stage and young), fertility-sparing cytoreductive surgery can be safely offered, especially with the knowledge that these cancers tend to be highly sensitive to chemotherapy. However, fertility-sparing surgery that results in residual disease being present at the conclusion of surgery is an area of potential controversy. The presence of residual tumor after cytoreductive efforts has been established to be a significantly

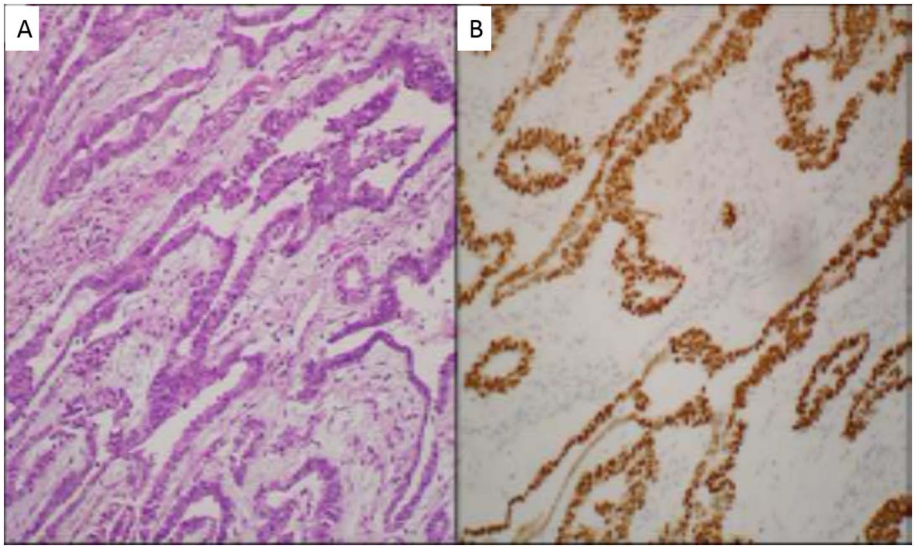

Fig. 2. Yolk sac tumor, endometrioid glandular type: (A). microscopic image showing tubular glands with marked nuclear atypia unusual for an epithelial tumor (H & E stain, 200 ×). (B) Immunostain for SALL-4 indicating germ cell origin (200 ×). Additional stains showed positivity for Glypican-3 and AFP and negativity for Oct-4, confirming yolk sac lineage (not shown).

poor prognostic factor. In patients with recurrent MOGCT, there is evidence to support that salvage surgery with optimal surgical cytoreduction increases survival.(Li et al., 2007) This remains an option for patients and therefore was offered to our patient.

The choice of chemotherapeutic agents for treatment of ovarian germ cell tumors have paralleled those studied in men with testicular germ cell tumors. The use of BEP for women with MOGCTs was studied in Gynecologic Oncology Group Trial 78.(Williams et al., 1994) In this protocol, patients with Stage I, II, or III completely resected ovarian germ cell tumors were given 3 courses of adjuvant BEP followed by optional re-assessment laparotomy. Ninety-three patients were enrolled. Follow-up duration ranged from 4 to 93 months, with 67 of the patients having > 2-year follow-up. Eighty-nine of the 93 patients were cancer free at the conclusion of the study. Two patients subsequently went on to develop secondary malignancies – 1 patient with acute leukemia and another with malignant lymphoma. No treatment-related deaths were noted. Toxicities were as expected from previous reports of patients treated with BEP for testicular cancer – myelosuppression, mucocutaneous toxicity, and febrile neutropenia. The authors concluded that administration of 3 cycles of adjuvant BEP in patients with completely resected MOGCT will almost always prevent recurrence. From these data, adjuvant BEP became the standard of care therapy for such patients.

Unfortunately, there exists little evidence to guide the management of patients that fail these initial therapies due to the rarity of this disease. Good quality data to guide management are lacking and treatment recommendations are also extrapolated from larger experiences with men with testicular cancer. In a large retrospective review by Einhorn, et al., the use of high-dose chemotherapy and stem-cell rescue for treatment of men with metastatic testicular cancer who had progressed after receiving cisplatin-based combination chemotherapy regimens was examined.(Einhorn et al., 2007a) For this regimen, patients were given 2 consecutive courses of high-dose chemotherapy with 700 mg/m^2 of carboplatin and 750 mg/m^2 of etoposide intravenously each for 3 consecutive days prior to the infusion of peripheral-blood stem cells. Most patients who showed signs of complete or partial response after these 2 high-dose courses were maintained on oral etoposide (50 mg/m^2) for 3 cycles. At a median follow-up time of 48 months, 116 out of 184 patients had complete disease remission without relapse. To our knowledge, there is no data on the use of high-dose chemotherapy with rescue stem cell transplant in patients with platinum-resistant ovarian germ cell tumors.

In 2015, Reddy Ammakkanaver et al. reported on a series of 13 patients with recurrent MOGCTs who were treated with high-dose salvage chemotherapy from 1990 to 2013. (Reddy Ammakkanaver et al., 2015) All patients in this series were initially treated with combination platinum-based chemotherapy. These patients received one dose of VeIP (Vinblastine, Ifosfamide, and Cisplatin) followed by the high-dose salvage chemotherapy and stem cell transplant regimen as described for our patient. In this series, the majority of treated patients had yolk sac tumors. Median survival was 11 months (with a range of 4 to 270 months). This series represents the largest series of patients treated with this type of therapy for MOGCTs.

Other active agents in the setting of recurrences include ifosfamide, taxanes, gemcitabine, and oxaliplatin. In a phase II trial, Einhorn et al. showed that a combination therapy of gemcitabine and paclitaxel was able to achieve an objective response rate of 31% in patients who progressed after both cisplatin combination chemotherapy followed by high-dose chemotherapy with tandem transplant.(Einhorn et al., 2007b) In a report from the German Testicular Cancer Study Group, 31 patients with recurrent germ cell tumors were treated with a combination of gemcitabine and oxaliplatin, with a 46% response rate noted. (Kollmannsberger et al., 2004).

In this report, we present a case of a woman with relapsed platinum-refractory endodermal sinus tumor who was successfully salvaged with high-dose chemotherapy and stem cell-rescue regimen shown to be successful in patients with relapsed testicular cancer. In our patient, as demonstrated in men with testicular cancer, a durable and complete response was obtained. While greater generalities and treatment recommendations cannot be made from just this one patient, this case underscores the similarities in treatment response across testicular and ovarian germ cell tumors. In rare cases of recurrent MOGCT such as this, we advocate for patient referral to tertiary specialty centers for consideration of aggressive and novel treatments strategies that otherwise may not be available to them.

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