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Case report

A case of metastatic dysgerminoma treated with two cycles neoadjuvant chemotherapy followed by fertility-sparing minimally invasive surgery

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1. Introduction

Ovarian germ cell tumors (OGCTs) account for only 5% of malignant ovarian neoplasms, with dysgerminomas being the most common type. Approximately 75% of dysgerminomas occur between the ages of 10–30 years (Scully et al., 1998). While pure dysgerminomas secrete no hormones, greater than 50% have elevated lactate dehydrogenase (LDH) and placenta alkaline phosphatase. Up to 5% produce β-hCG due to the presence of syncytiotrophoblasts (Kawai et al., 1992). The majority of dysgerminomas are stage I at diagnosis, and are appropriately treated with fertility-sparing surgical staging (Gordon et al., 1981).

Upfront fertility-sparing surgery even with later stage disease is common due to the uniquely chemosensitive nature of OGCTs, with dysgerminomas being the most chemosensitive (Low et al., 2000). The chemotherapy regimen of choice is bleomycin, etoposide, and cisplatin (BEP), based on Gynecologic Oncology Group (GOG) protocols 45 and 90 and two follow up studies (Williams et al., 1991; Gershenson et al., 1990; Brewer et al., 1999). A later study in 2001 demonstrated that in good-prognosis germ cell cancer three cycles of BEP is sufficient and administration of chemotherapy in three days is equally effective to five days (de Wit et al., 2001).

While most advanced stage cases are treated with primary cytoreduction and adjuvant chemotherapy, neoadjuvant chemotherapy (NACT) could be used to avoid aggressive initial surgical intervention. We present a case of a critically ill 18-year-old with metastatic dysgerminoma deemed unresectable who was treated with a limited course of NACT followed by laparoscopic unilateral salpingo-oophorectomy.

2. Case report

An 18-year-old nulligravid presented with two weeks of abdominal pain, early satiety, and bloating. A computed tomography (CT) scan demonstrated a 20 × 7 × 21 cm abdominopelvic mass extending from sidewall to sidewall and bilateral pleural effusions. Labs were notable for LDH 42,000 units/L, uric acid 13 mg/dL, β-hCG 4700 mIU/mL, normal AFP, and a metabolic acidosis with bicarbonate of 11 mEq/L. She received rasburicase for elevated uric acid levels and was transferred to our institution. Pelvic magnetic resonance imaging (MRI) was performed and showed an extensive soft tissue mass likely arising from the left ovary and filling most of the peritoneal cavity, with thickening of the peritoneum and enlarged right obturator lymph nodes concerning for metastases (Fig. 1). Ultrasound-guided biopsy confirmed the diagnosis of dysgerminoma (Fig. 2). Given a potentially unresectable tumor in a critically ill patient, the decision was made to immediately treat with NACT with (BEP). Due to her large tumor burden and concern for tumor lysis syndrome (TLS), the patient was placed on telemetry, given brisk intravenous fluid hydration, started on allopurinol, and given BEP over 5, rather than 3 days, with etoposide 100 mg/m^2 and cisplatin 20 mg/m^2. On day 2 she developed new-onset somnolence and worsening metabolic acidosis with a pH of 7.16 necessitating transfer to the intensive care unit (ICU) and a bicarbonate drip. Her TLS worsened over the next 4 days, creatinine rose to 2.14 and thus cisplatin was held. Carboplatin with area under the concentration (AUC) of 2 was administered instead on cycle days 4 and 5. By the time of discharge, her respiratory status had normalized, metabolic acidosis had resolved, and creatinine was improving.

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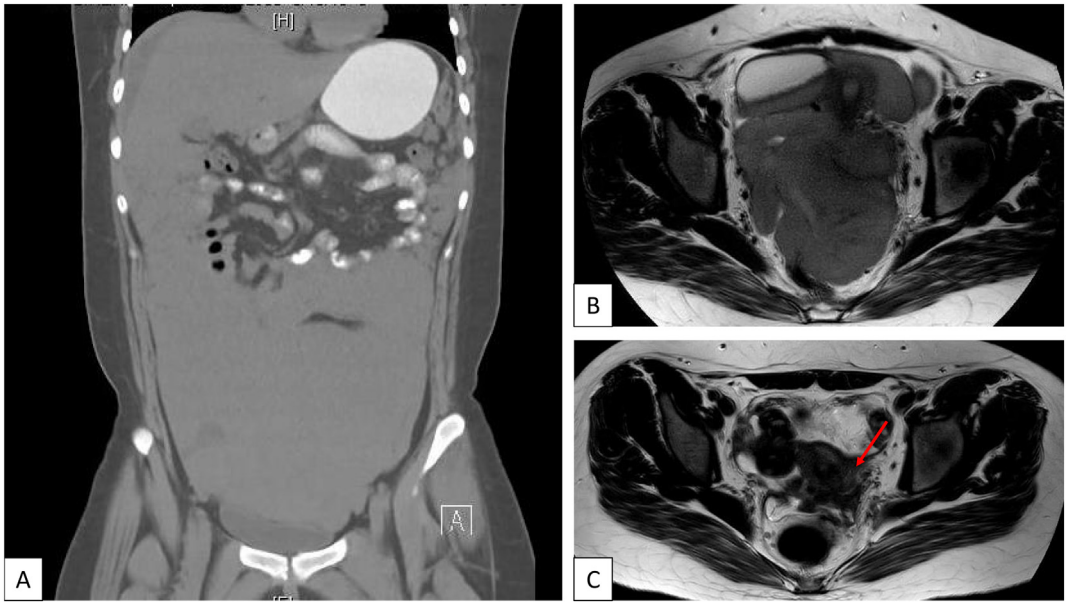


Fig. 1. Magnetic resonance imaging (MRI). A coronal view at diagnosis shows extension to liver B axial view at diagnosis demonstrates the mass filling the pelvic cavity with unclear origin. C: After 2 cycles of neoadjuvant chemotherapy axial view shows normal-appearing uterus and ovaries and a 1.3 cm residual mass in the left adnexa (arrow).

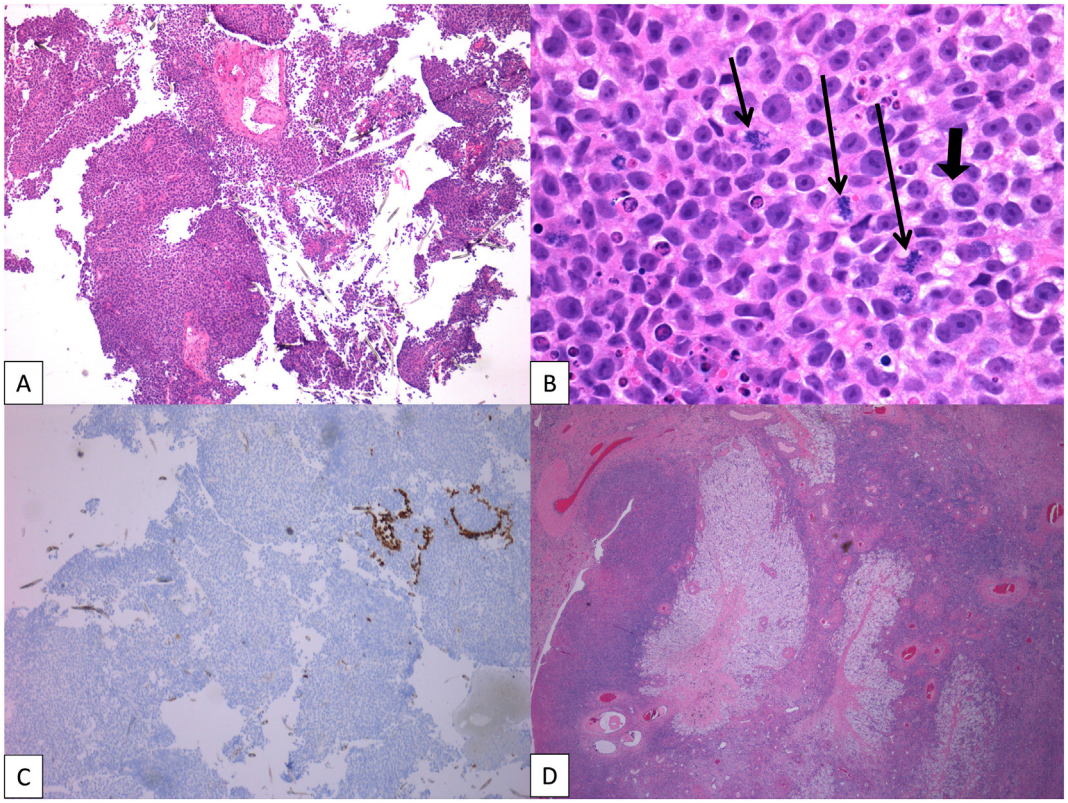
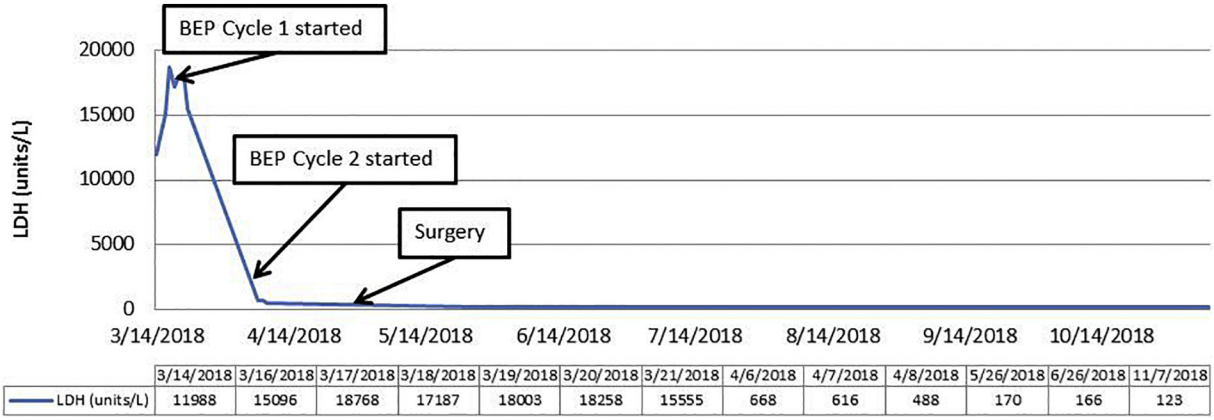


Fig. 2. Morphological features of the pre-treatment biopsy and from surgery (hematoxylin and eosin stain unless otherwise specified). A: Low-powered view of pre-treatment biopsy showing dysgerminoma. B: High-powered view of the pre-treatment biopsy shows sheets of uniformly medium sized cells with somewhat well-defined cell borders, eosinophilic to clear cytoplasm (block arrow), centrally located nuclei with prominent nucleoli, and numerous mitoses (thin arrows). C: Lack of pan-cytokeratin immunohistochemical expression on the pre-treatment biopsy (along with positivity for OCT3/4 and negativity for CD30, not shown). D: After treatment, left ovary shows extensive treatment effect with no viable dysgerminoma or normal ovarian tissue.

When the patient was readmitted for cycle 2 of BEP her abdominal pain had resolved, abdominal girth had decreased, and creatinine had normalized. BEP was administered uneventfully over 3 days, with etoposide 165 mg/m^2 and cisplatin 50 mg/m^2. MRI after cycle 2 showed a dramatic interval improvement with near-complete resolution except for a 1.3 cm soft tissue nodule in her pelvis (Fig. 1). Decision was made to proceed with surgery for curative intent and to minimize chemotherapy exposure. Pre-operative LDH was 488 units/L and β-hCG



	3/14/2018	3/16/2018	3/17/2018	3/18/2018	3/19/2018	3/20/2018	3/21/2018	4/6/2018	4/7/2018	4/8/2018	5/26/2018	6/26/2018	11/7/2018
LDH (units/L)	11988	15096	18768	17187	18003	18258	15555	668	616	488	170	166	123

Fig. 3. Trend of lactate dehydrogenase (LDH) levels (units/L) throughout the patient's treatment course.

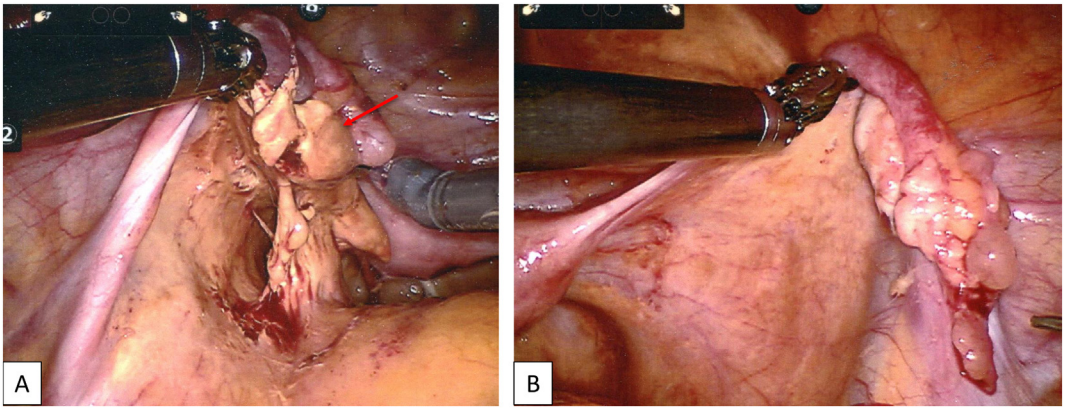


Fig. 4. Intraoperative findings during interval robotic-assisted left salpingo-oophorectomy. A: Left ovary encased in necrotic fatty tissue (arrow) adherent and continuous with the left pelvic sidewall. [B] Normal-appearing right ovary.

was 3 mIU/mL (Fig. 3). The patient underwent an uncomplicated robotic-assisted laparoscopic left salpingo-oophorectomy and peritoneal biopsies. Intraoperative findings were notable for fatty appearing infiltration of the left ovary, the pelvic peritoneum, and the surface of the sigmoid colon, and otherwise a visually normal right ovary, uterus, omentum and upper abdominal peritoneal survey (Fig. 4). Final pathology showed abundant hyalinization, hemorrhage, pigment deposition and foamy macrophages consistent with treatment effect and no residual neoplasm as well as no normal residual left ovarian tissue (Fig. 4). Pelvic washings were negative.

Due to symptoms of neuropathy and tinnitus and the lack of residual disease at surgery, her regimen was changed to carboplatin and etoposide for two additional cycles. After completing adjuvant chemotherapy, her LDH was normal at 166 units/L and b-hCG was 3 mIU/mL. At 6 months follow up, LDH was 123 units/L and right ovarian ultrasound was normal.

3. Discussion

Our patient presented with a massive dysgerminoma filling the abdominal cavity from side to side, and from coccyx to liver making it questionable whether abdominal entry would be possible. Additionally, the patient was critically ill on transfer with uremia and acidosis. We feared delaying chemotherapy with a possibly unsuccessful laparotomy and made the decision to proceed urgently with NACT. To our knowledge, this is the first report of just two cycles of NACT for dysgerminoma. Her remarkable response allowed for a minimally invasive approach after only two cycles of chemotherapy and facilitated a fertility-sparing surgery. While the patient had a near complete radiologic response to chemotherapy after only two cycles, we did not want to skip surgery entirely. Remarkably, even the small residual pelvic mass turned out not to have viable neoplasm nor residual ovarian tissue. The indication for primary comprehensive surgical staging is supported in the literature, with data showing that patients who do not undergo primary surgery have higher rates of disease recurrence (Lin et al., 2014).

Rarely OCGT size, location, co-morbidities and spread patterns may preclude a primary surgery. In such cases, consideration of NACT is appropriate. Several studies have shown that residual tumor after cytoreductive surgery has a negative impact on overall survival suggesting a role for NACT (Lai et al., 2005; Lee et al., 2011). In a series of NACT for OCGT, Talukdar et al. presented 23 cases from 1988 to 2009 in which patients with stage III and IV malignant OCGT received four cycles of BEP NACT(Talukdar et al., 2014). Dysgerminomas accounted for 14 cases. Twenty-one patients with OGCT experienced either a complete response (CR) or partial response (PR), of whom 12 had dysgerminoma. Of these 21 patients, 18 underwent surgery, all with fertility-preservation. All 21 are alive and disease-free. Authors compared this to 43 cases over the same time period that were treated with surgery followed by chemotherapy. They found that 30 (69%) underwent fertility-sparing surgery. Thirty-four patients had greater than 2 cm of residual tumor. Of these 43 patients, 30 were alive and disease-free at analysis (Talukdar et al., 2014). Their findings suggest that NACT not only resulted in better survival, but greater rate of fertility preservation.

A Children's Oncology Group study concluded in 2004 that patients with advanced disease refractory to surgical management could be treated with four cycles of NACT followed by surgery (Billmire et al.,

2004). Our patient had a complete pathologic response after only two cycles of BEP, as compared to the four cycles described, and was able to undergo fertility sparing minimally invasive surgery. The minimally invasive approach allowed the patient to continue her chemotherapy on time. Our case supports the use of less NACT in patients with metastatic dysgerminoma, provided there is careful clinical assessment of treatment response to time surgery.

Clinical factors in this case increased our patient's risk of TLS. She demonstrated evidence of TLS prior to chemotherapy with an elevation in uric acid and we suspected that chemotherapy would worsen this condition. We therefore gave BEP over five days instead of three in hopes of minimizing renal injury and to allow flexibility in dose adjustments as toxicities became apparent. TLS is an oncologic emergency that occurs when rapid cell lysis releases large quantities of potassium, phosphate and nucleic acids into the circulation resulting in hyperuricemia, hyperphosphatemia, and possible acute kidney injury due to deposition in renal tubules. Risk factors for TLS include chemosensitivity; high cell proliferation rate; large tumor burden with size greater than 10 cm, and hyperuricemia or LDH greater than twice the upper limit of normal (Baeksgaard and Sorensen, 2003). Maintaining high urine output levels and controlling uric acid and phosphorous levels are important components of TLS management. Patients at risk should have strict monitoring of fluids, electrolytes, creatinine and uric acid. Aggressive intravenous hydration is important and rasburicase and/or allopurinol can be used to control elevated uric acid levels (Finkel and Howard, 2014). Our patient was given rasburicase prior to treatment and allopurinol concurrent with initiation of chemotherapy.

In summary, while primary surgery is the standard of care for most cases of dysgerminoma, NACT is reasonable in patients whose tumors are not conducive to upfront surgery. When considering NACT it is important to evaluate the risk of TLS and manage patients aggressively to decrease the severity of these complications. Treatment response can be evaluated with each cycle of chemotherapy by symptoms, tumor markers, physical exam, and imaging to determine the earliest reasonable time for surgery. This case demonstrates that depending on tumor response it is feasible and can be advantageous to administer only two cycles of NACT with BEP, as compared to the four cycles commonly described in the literature, and then proceed with minimally invasive fertility sparing surgery. Given her advanced disease at presentation, we will closely follow our patient for recurrence by serial imaging of her contralateral ovary and testing her tumor markers every six months for several years.

Conflict of interest statement

The authors have no conflicts of interest to report.

Author contribution section

KE drafted and revised the manuscript. ES and EW revised the manuscript. MT and LK provided the images. All authors have given final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

Patient consent

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.

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