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Case report

Pure ovarian dysgerminoma in a postmenopausal patient: A case report and review of the management

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ABSTRACT

Background: A pure ovarian dysgerminoma in a postmenopausal female is a rare phenomenon.
Case: A 65-year-old female presented with a large pelvic mass. Following surgical debulking, the patient was diagnosed with FIGO Stage IIB ovarian dysgerminoma. She was treated with three cycles of etoposide and cisplatin and has been disease-free for 12 months.
Conclusion: Dysgerminomas in postmenopausal females are uncommon. Gynecologic oncologists should be familiar with the pathological diagnosis and treatment recommendations to achieve optimal outcomes.

1. Introduction

Malignant ovarian germ cell tumors (OGCT) account for 2–5% of all ovarian neoplasms. Dysgerminomas compose half of all malignant ovarian germ cell neoplasms and is the female equivalent of seminoma (Barakat, 2013). The median age at diagnosis is between 16 and 20 years (Barakat, 2013). Most dysgerminomas occur before the age of 40, with 75% presenting between ages 10 and 30 years (Barakat, 2013; Bailey and Church, 2005). Compared to other OGCT, dysgerminomas are usually diagnosed at an early stage and 10% of cases have bilateral ovarian involvement (Barakat, 2013). Dysgerminomas are associated with an excellent prognosis, due to their sensitivity to both chemotherapy and radiation (Barakat, 2013; Solheim, 1990). Overall survival for patients with dysgerminoma decreases with increasing age based on data from the Surveillance, Epidemiology and End Results (SEER) program. (Barakat, 2013; Solheim, 1990). Solheim et al. found that the risk of death increases ninefold for women over 40 years of age. Other factors associated with poor survival include low socioeconomic class and metastases at presentation, with the latter often found in postmenopausal patients (Solheim, 1990). OGCT is overall rare in postmenopausal patients, more data among this population is necessary to determine optimal treatment strategies and outcomes. We present a case of pure dysgerminoma in a postmenopausal patient.

2. Case

A 65-year-old, healthy, Caucasian, gravida 3 para 3 female presented to her primary gynecologist with urinary frequency and pelvic fullness. She denied nausea, vomiting, or vaginal bleeding. She reported no prior use of hormonal therapy. Her only surgery was 20 years ago, which was a total laparoscopic hysterectomy for persistent cervical dysplasia. Her medical conditions included hypertension, hyperlipidemia, and arthritis. Recent mammogram and colonoscopy were normal. Family history was significant for breast, colorectal, prostate, and bladder cancers. She reported no family members had genetic testing and no known history of Ashkenazi Jewish ancestry.

Physical exam revealed a firm, palpable, lower abdominal mass. Transvaginal ultrasound and CT of the abdomen and pelvis revealed a lobulated, solid 15 × 14 × 12 cm mass arising from the pelvis and extending cephalad to the umbilical level (Fig. 1A). CT scan of the chest illustrated minimal right pleural effusion but was otherwise unremarkable. Preoperatively, cancer antigen 125 (CA125) was elevated to 182 U/ml. Carcinoembryonic antigen (CEA) and cancer antigen 19–9 (CA19-9) were normal. No other tumor markers were obtained.

The patient was referred to gynecologic oncology and underwent an exploratory laparotomy. Intraoperative findings included a 19.5 cm solid left ovarian mass adherent to the left pelvic sidewall and pelvis (Fig. 1B), normal appearing right tube and ovary, miliary tumor deposits (1–5 mm in diameter) in anterior and posterior cul-de-sac, and enlarged

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lymph nodes bilaterally in the pelvic, obturator, and *para*-aortic regions. A thorough exploration of her abdomen was performed and revealed no other evidence of metastatic disease. A complete bilateral salpingo-oophorectomy, bilateral pelvic and *para*-aortic lymph node dissection, omentectomy, and radical tumor debulking to R-0 was subsequently performed. Her postoperative recovery was uncomplicated.

Serial sectioning of the ovary showed a tan-yellow-colored tumor mass with lobulated architecture with areas of hemorrhage and extensive necrosis with cystic degeneration (Fig. 1C). Histologic examination revealed nests of large, uniform polygonal cells with clear to eosinophilic cytoplasm and distinct cell membranes. Areas of high mitotic activity noted (Fig. 1E). The tumor was separated by fibrous septae containing lymphocytes and epithelioid histiocytes. (Fig. 1F). Tumor involvement was found in the left anterior pelvic peritoneum and posterior cul-de-sac (Fig. 1D). Immunohistochemical (IHC) stains showed diffuse intense membrane staining for CD117 (Fig. 1G), SALL-4 (Fig. 1H), and OCT3/4 (Fig. 1I). A total of 9 lymph nodes were removed which were negative for malignancy. Based on these findings the patient was diagnosed with FIGO Stage IIB ovarian dysgerminoma. The tumor cells were positive for PD-L1 biomarker with a combined positive score of 10 (test performed at Caris Life Science™) with low tumor mutational burden (TMB) score of 4 mutations per megabase with proficient microsatellite instability (MSI), negative estrogen receptor (ER), and negative progesterone receptor (PR). Genetic testing of 47 genes with the Invitae Common Hereditary Cancers + RNA panel™ and Common Hereditary Cancers Genes Eligible for RNA Analysis™ did not identify any pathogenic variants known to cause carcinoma.

Adjuvant chemotherapy was initiated three weeks after surgery based on data from GOG 45 (Williams, 1989) and GOG 78 (Williams, 1994). Cisplatin 20 mg/m2 IV administered on days 1–5 and Etoposide 100 mg/m2 IV days 1–5 repeated every 21 days for 3 cycles over fifty-eight days. The patient declined Bleomycin administration. No dose reductions required. Primary toxicities were grade 1 neuropathy and ototoxicity. CT abdomen/pelvis after completion of chemotherapy showed no evidence of disease. The patient recently completed a year of surveillance which included physical exams, serum tumor markers (CA125 and LDH), and CT imaging with all indicating no evidence of recurrent disease.

3. Discussion

To our knowledge, this is one of the few case reports of pure dysgerminoma in a postmenopausal woman. In the largest case series of ovarian germ cell tumors in postmenopausal women, only one patient had a pure dysgerminoma (Boussios, 2015). The incidence of dysgerminomas in postmenopausal women is unknown. Malignant ovarian germ cell tumors, including a dysgerminoma, in this age group, are rarely considered in the differential diagnosis of an ovarian mass. Symptoms of ovarian dysgerminoma are non-specific. Abdominal pain, pelvic pain, and urinary symptoms are the most common symptoms. Serum tumor marker testing in postmenopausal women usually include serum CA-125 and CEA. Ovarian germ cell tumor marker testing including AFP, HCG, and LDH would not be routinely obtained to assist with the diagnosis of an ovarian mass in this age group. Ultrasound imaging of a dysgerminoma may demonstrate a septate ovarian mass with varying echotexture, and CT scan may illustrate a multilobulated solid mass with prominent fibrovascular septa (Zhao et al., 2020).

The pathological features of dysgerminomas are unique. H&E staining can show a variety of architectural patterns. Most notably, as in our case, the neoplastic cells can express significant mitotic activity in the background of fibrous septate with an abundance of lymphocytes (Clement, 2020). Due to tumor rarity, histologic features are not known

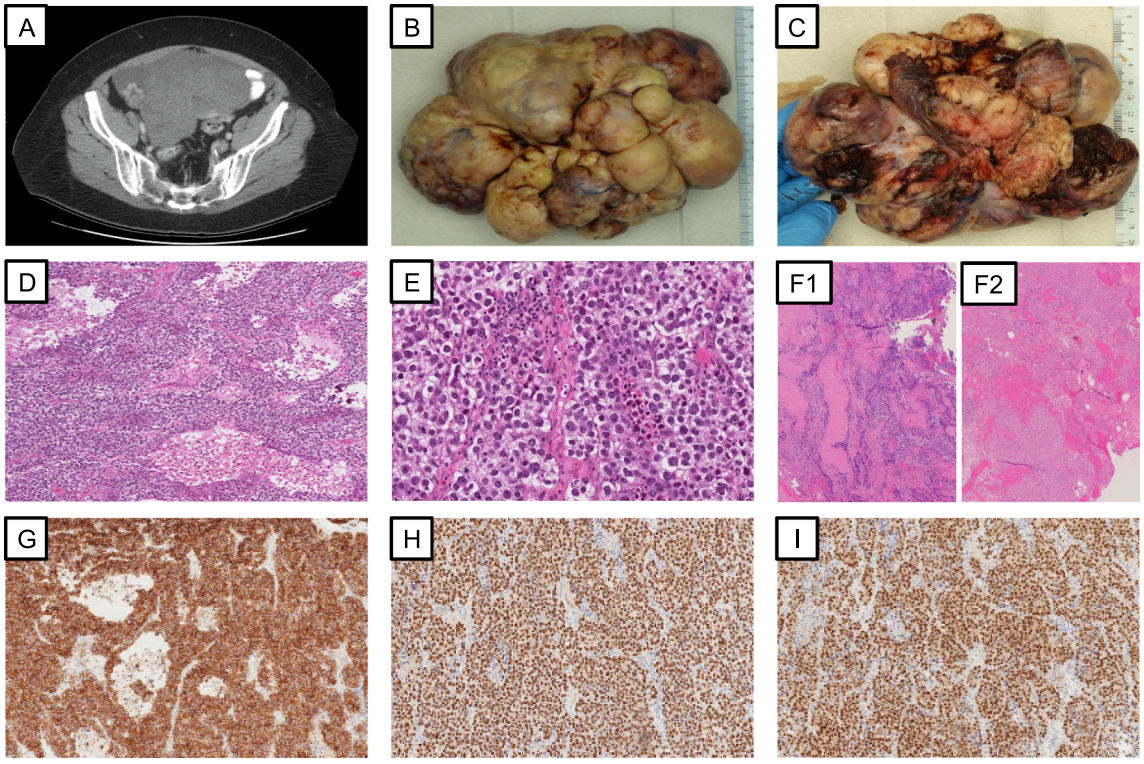

Fig. 1. Radiology and Pathology Findings (A–I). Preoperative radiographic image of CT abdomen/pelvis showing a bulky lobulated mass arising from the pelvis and extending cephalad to the umbilical level (1A), gross image of 19.5 cm tan-yellow lobulated mass encompassing left ovary (1B), cross section of tumor showing areas of hemorrhage and abundant necrosis (1C), hematoxylin and eosin (H&E) at low power shows nests of large, uniform polygonal cells with pale cytoplasm and distinct cell membrane with brisk mitosis, and extensive necrosis (1D), H&E at high power showing tumor cells separated by fibrous septate in an alveolar pattern containing lymphocytes, plasma cells, and eosinophils (1E), H&E at low power shows metastasis in peritoneum (1F1) and posterior cul-de-sac (1F2), IHC staining of tumor cells show strong membranous staining with CD117 (1G) and strong nuclear staining with SALL4 (1H), and OCT3/4 (1I).

to provide any prognostic value. Immunohistochemical staining plays a key role in identifying a dysgerminoma from other germ cell tumors and clear cell carcinomas. Typically, cells of dysgerminomas express CD117, OCT 3/4, and SALL4 (Kaspar and Crum, 2015). In our patient, the histology findings and immuno-profiling confirmed a diagnosis of a dysgerminoma.

Surgery staging is required for definitive diagnosis and to guide the need for adjuvant therapy. Fertility preserving surgery is reasonable in young women but is not recommended for patients who have completed child-bearing (Barakat, 2013). A midline incision with a thorough inspection of the peritoneal cavity followed by a total hysterectomy, bilateral salpingectomy-oophorectomy, paraaortic and bilateral pelvic lymph node dissection, and omentectomy is performed. After surgical staging, all patients, except patients with stage IA pure dysgerminomas, should receive adjuvant chemotherapy. Adjuvant chemotherapy is recommended based on several small studies including results from treatment of testicular seminomas (Williams, 1989; Williams, 1994; Network and Cancer, 2022; Funt et al., 2021). Randomized clinical trials to assess the benefits of various chemotherapy modalities cannot be completed due to the rarity of ovarian dysgerminomas. The National Comprehensive Cancer Network (NCCN) guidelines endorse a multi-chemotherapy regimen of bleomycin, etoposide, and cisplatin (BEP) as the initial treatment for a FIGO Stage IB – IVB ovarian dysgerminoma (Network and Cancer, 2022).

In 1989, GOG 45, a nonrandomized prospective trial of Cisplatin, Vinblastine, and Bleomycin (PVB) was administered to patients with previously resected advanced OGCT. Results indicated cisplatin-based chemotherapy had a 51% 2-year progression free survival (PFS) and 71% overall survival (OS) (Williams, 1989). This study showed cisplatin had curative potential. A subsequent trial, GOG 78 in 1994, performed a nonrandomized prospective trial of BEP after surgical staging for ovarian dysgerminomas. This study found 89/93 patients remained disease free of OGCT at the second look surgery (Williams, 1994).

The primary irreversible side effect with the BEP regimen is bleomycin induced pulmonary fibrosis due to the minimal quantity of the protective hydrolase enzyme in lung tissue (Sikic, 1986). Studies indicate bleomycin lung injury is more common in older patients and patients with renal insufficiency. An alternative treatment option for patients with a good prognosis CGTS is etoposide and cisplatin (EP). A study by Funt and colleagues found EP regimen in patients with testicular cancer had a 5-year PFS 93.9% and OS of 97.9% (Funt et al., 2021). We recommended to this patient adjuvant etoposide and cisplatin without bleomycin. To date, no randomized trials have been completed comparing BEP vs EP in ovarian dysgerminomas. Substitution of carboplatin for cisplatin is another alternative treatment regimen endorsed in the NCCN guidelines (Williams et al., 2004). Patients with complete resection of ovarian dysgerminomas, FIGO stage IB-III, treated with etoposide and carboplatin had low recurrence rates. The study did not meet accrual goals before closing enrollment of patients (Williams et al., 2004).

We recommended three cycles of EP for two reasons. First, she had an increased risk of pulmonary fibrosis related to bleomycin therapy due to her age. Second, she had favorable factors including complete surgical removal of tumor and stage IIB disease. The decision to administer three cycles vs four cycles of EP was based on a study published by Wit and associates. This study compared three versus four cycles of BEP in patients with ovarian dysgerminomas. Patients receiving three cycles reported better overall quality of life, including physical functioning, role functioning, cognitive functioning, fatigue, and nausea/vomiting (de Wit et al., 2001). Patients who develop recurrent disease after surgery and adjuvant chemotherapy have alternatives. One regimen is a combination of paclitaxel, ifosfamide, and cisplatin (TIP) (Network and Cancer, 2022). Immunotherapy may offer another treatment option for patients with recurrent OGCTs. A recent phase II clinical trial of Pembrolizumab in patients with advanced, heavily pretreated metastatic germ cell tumors, immunotherapy agent was well tolerated but robust antitumor activity was lacking (Tsimberidou et al., 2021).

4. Conclusion

Pure dysgerminomas in postmenopausal patients are uncommon. We report a unique case of dysgerminoma successfully treated with surgery and adjuvant chemotherapy. The rarity of ovarian dysgerminomas makes patient accrual to randomized phase III trials problematic. The optimal adjuvant chemotherapy is unknown. A combination of etoposide with either cisplatin or carboplatin for 3–4 cycles is a reasonable treatment regimen for most patients.

5. 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 upon request.

Author contribution

JV, AM, and BB contributed to the literature search. JV and AM drafted the manuscript. NO, TC, NP performed the pathologic evaluation and provided the pathologic figures. RR provided input regarding chosen adjuvant therapy. JS, RH, BR provided revised the manuscript. All authors critically reviewed, edited, and approved the final manuscript for publication.

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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