

Case Report

Desmoplastic small round cell tumor of the ovary: A rare but devastating disease in young women [☆]John Nakayama ^{a,*}, Sarah Nassau ^b, Kristen Atkins ^b, Susan C. Modesitt ^a^a University of Virginia Medical Center, Division of Gynecologic Oncology, Dept. of OB/GYN, PO Box 800712 Charlottesville, VA 22908, USA^b University of Virginia Medical Center, Dept. of Pathology, PO Box 800904 Charlottesville, VA 22908, USA

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Introduction

Desmoplastic small round cells tumor (DSRCT) is a rare intra-abdominal neoplasm. It is primarily found in young men with a reported male to female ratio of four to one (Ota et al., 2010). Common presenting symptoms include abdominal pain and distension. Unfortunately, DSRCT is often widely disseminated throughout the peritoneal cavity at diagnosis and quickly recurs despite treatment so prognosis is exceedingly poor.

Given the male predominance of this disease, DSRCT rarely enters the differential diagnosis in young women with an ovarian mass; however, it is important to keep DSRCT in mind as it may influence how aggressively one chooses to surgically treat a patient with an unusual pelvic mass. This study's objective was to provide an overview of this uncommon disease, add three cases (including a 6-year-old girl) to the previously reported 12 and review the literature for treatment recommendations.

Case reports

Case 1

A 6-year-old female presented to a local hospital with intractable abdominal pain (previously diagnosed as constipation) that was

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associated with fever and tachycardia. A computed tomography (CT) showed multiple pelvic masses, enlarged para-aortic lymph nodes, and a liver hypodensity concerning for a neoplasm. The patient was transferred to a tertiary care center for further evaluation. Upon arrival, serum tumor markers, HCG and AFP, were normal (CA-125 not done), and she underwent a diagnostic laparoscopy which revealed bilaterally enlarged ovaries with several 1–3 cm masses in the cul-de-sac that were biopsied. Microscopy demonstrated islands of primitive small round blue cells in a fibroblastic stroma with abundant necrosis and scattered calcifications (Fig. 1). The tumor was mildly pleomorphic and composed of small cells with hyperchromatic nuclei, irregular nuclear contours and clear cytoplasm. Immunohistochemistry was strongly reactive for desmin, pan-cytokeratin, NSE, CD56, and EMA, and showed focal immunoreactivity for CD99, NB-84a, and bcl-2. The tumor cells were negative for FLI-1, S-100, myogenin, and LCA. Cytogenetic testing showed an Ewing sarcoma (EWS) gene disruption in the majority of her tumor cells (Fig. 2). The morphology, immunohistochemistry and cytogenetic findings were all consistent with the diagnosis of DSRCT.

After surgery, further evaluation revealed bone marrow, liver, and retroperitoneal lymph node involvement; additionally a PET scan confirmed mediastinal, peri-pancreatic, mesenteric, and retroperitoneal spread. The patient's care was transferred to a regional center specializing in DSRCT where she received the P6 regimen: seven cycles of the sarcoma chemotherapy regimen IE/VDC (Ifosfamide, Etoposide, Vincristine, Adriamycin, and Cytoxan) chemotherapy. She progressed in 3 months with leptomeningeal metastases. After 3600 cGy of craniospinal radiation with a 540 cGy boost to the brain and TMZ-CPT-11 for 12 cycles, she was disease free. However, the patient recurred 11 months later and progressed through 4 months of cyclophosphamide, vinorelbine, and bevacizumab. She was placed on a phase I trial of IMC-A12 and temsirolimus without response. The patient expired 28 months after her initial diagnosis.

Case 2

A 28-year-old female presented with one month of abdominal pain and pressure. CT showed multiple abdominopelvic masses, mesenteric lymph nodes, and a peri-splenic mass. CA-125 was 42 U/mL. Biopsy results were consistent with DSRCT, and she received 14 cycles of neoadjuvant IE/VDC with the removal of adriamycin after the eighth cycle due to cardiac toxicity. Following an incomplete response, the patient underwent an exploratory laparotomy. Intra-operative findings included a 10 × 8 cm right ovarian cystic mass, an 8 cm nodule

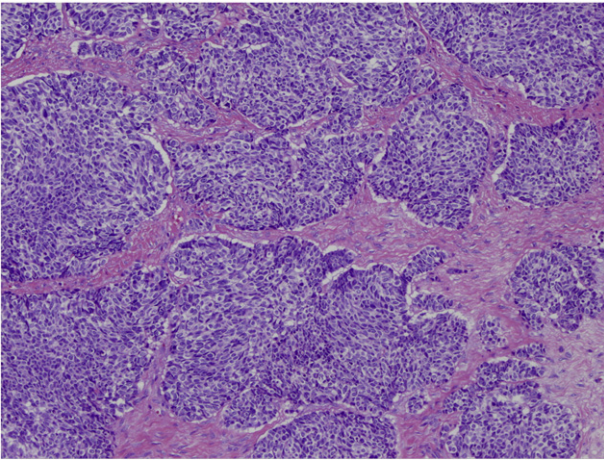


Fig. 1. Microscopic appearance of DSRCT: Islands of small round blue cells surrounded by fibroblastic stroma.

between the stomach and the spleen and small implants in the cul-de-sac and omentum. A bilateral salpingo-oophorectomy, resection of cul-de-sac peritoneum, and splenectomy, and omentectomy were performed leaving her without visible disease. Microscopy showed cords of small round blue cells. Immunohistochemistry revealed strong and diffuse positivity for desmin and multifocal keratin positivity. CD99 was negative. Cytogenetics was negative for the EWS-WT1 translocation.

She returned on post-operative day 5 with a fascial dehiscence which was repaired without complication. The patient finished the last 2 cycles of her 16 cycle chemotherapy regimen and did well for 6 months. At that time, a CT showed increased abdominopelvic disease and a bone scan was consistent with metastasis. She was started on cytoxan/topotecan which she received from her local oncologist. The patient expired of her disease 40 months after her initial diagnosis.

Case 3

A 17-year-old female presented with several months of increased abdominal girth associated with pelvic pain and nausea. Ultrasound showed a 10 cm right adnexal mass and ascites. Serum tumor markers were drawn and showed normal AFP, beta-HCG and LDH. CA-125 was 35.9 U/mL, and her inhibin was elevated to 481 pg/mL.

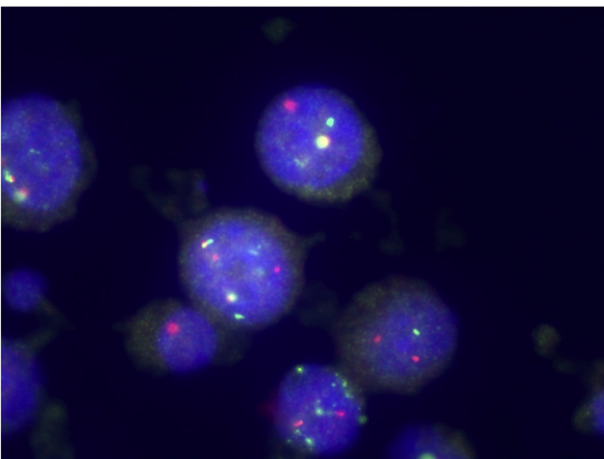


Fig. 2. Cytogenetic diagnosis of DSRCT: Fluorescent in situ hybridization for EWS (Ewing's sarcoma) gene and WT1 gene disruption. Yellow corresponds to an intact gene while red and green represent a disruption.

She underwent an exploratory laparotomy which found a 15 cm multicystic right ovarian mass with tumor implants on the left ovarian serosa, peritoneum, epiploica, liver, omentum and cul-de-sac. A right salpingo-oophorectomy, peritoneal stripping of the anterior cul-de-sac, appendectomy, and argon laser ablation of tumor nodules were performed. The patient was optimally debulked but visible sub-centimeter disease was present at the end of the procedure. Microscopy was consistent with DSRCT, and immunohistochemistry revealed tumor diffusely positive for keratin, desmin, p63, and focally positive for FLI-1. Stains were negative for S-100, WT-1, CD99, and inhibin. The cytogenetic studies were positive for the EWS-WT1 translocation. The patient is now status post 9 cycles of IE/VDC chemotherapy with interval debulking after seven cycles. She then received whole abdominal radiation with a pelvic boost. She is alive without disease at 11 months from her diagnosis.

Discussion

DSRCT is a rare clinical entity with only 12 prior reported cases in women in the English literature. Unfortunately, ovarian DSRCT presents early in life at an average age of 19 years and life expectancy ranges from 4 to 42 months (see Table 1) (Ota et al., 2010; Young et al., 1992; Zaloudek et al., 1995; Elhadj et al., 2002; Fang et al., 2008; Engohan-Aloghe et al., 2009). Common symptoms at presentation are an abdominal mass, constipation, pain, nausea/vomiting and weight loss (Fang et al., 2008; Church et al., 2006). CA-125 is often elevated with a wide reported range (35.9–2823 U/mL). Generally, only one ovary is involved with an average size of 11 cm, but most patients have widespread disease throughout the peritoneal cavity on presentation. The most common sites of metastasis are the liver, lymph nodes, lung and bone marrow (Church et al., 2006).

Histologically, DSRCT is characterized by small round cells with scanty cytoplasm in nests. The tumor cells are typically surrounded by dense desmoplastic cytoplasm which is an important characteristic suggesting the DSRCT diagnosis (Engohan-Aloghe et al., 2009). However, making a definitive diagnosis based on morphological characteristics alone is often not possible. The differential of small round tumor cells includes Ewing's sarcoma, rhabdomyosarcoma, primitive neuroectodermal tumor, lymphoma, adrenal neuroblastoma, and hepatoblastoma (Elhadj et al., 2002). Immunohistochemistry and cytogenetics are used to confirm the diagnosis. DSRCT has a characteristic co-expression of epithelial (keratin, epithelial membrane antigen), mesenchymal (vimentin, desmin), and neural antigens (neuron specific enolase) (Ordonez, 1998). Other stains which are often positive are WT-1, FLI-1, and CD99 (Fang et al., 2008). Staining negative for myogenin, MyoD1, chromogranin, HMB-45 and CD45 can also help to distinguish DSRCT from other forms of small round cell tumors. Additional confirmation of the DSRCT diagnosis is made via detection of the chromosomal translocation $t(11;22)(p13;q12)$. This translocation fuses the Ewing sarcoma gene (EWS) with the Wilms' tumor suppressor gene (WT1) to create a gene that likely acts as a transcriptional activator for pro-tumorigenic genes (Fang et al., 2008). However, the EWS-WT1 fusion is not always present (Ota et al., 2010).

Given the rarity of ovarian DSRCT, there is no consensus on treatment. Despite responding well to chemotherapy, tumors recur quickly and long term survival is poor. In a study of 66 patients (91% male) with general DSRCT, the overall 5-year survival rate was 15%. This study also showed that patients who received primary debulking surgery, multi-agent chemotherapy, and radiation had a significantly improved survival over those who did not receive all three modalities (3-year survival: 55% versus 27% $p < 0.02$) (Lal et al., 2005). There is also no gold standard chemotherapy regimen, but there is evidence that a high dose alkylator-based regimen improves survival (Kushner et al., 1996). The "P6 protocol," which is four cycles of cyclophosphamide, adriamycin and vincristine (VDC) with a cycle of

Table 1
Summary of the reported cases of ovarian DSRCT.

Case number	Age (years)	Ovarian involvement	CA-125 (U/mL)	Cytogenetic evidence	Initial treatment	Follow-up
1	15	9 cm and 8.5 cm unknown laterality. (masses solid)	Not done	Not done	Surgical debulking with multi-agent chemotherapy including carboplatin	Died 4 months
2	15	Right: 15 cm (solid/cystic) Left: 9 cm (solid)	Not done	Not done	Surgical debulking, no chemotherapy	Secondary debulking at 7 months
3	14	Right: 5.3 cm (solid)	Not done	Not done	Surgical debulking	None
4	22	Right: 8 cm (solid), Left: 6.5 cm (solid)	125	Not done	Surgical debulking, chemotherapy with BEP	Died at 18 months
5	11	Right: 12 cm (solid/cystic)	88.5	Note done	Surgical debulking, P6 and myeloablative chemotherapy	Died at 11 months
6	23	Right: 6.8 cm (solid)	140	Not done	Surgical debulking, platinum and taxol chemotherapy	None
7	27	Right: 13 cm, Left: 20 cm	Not done	Not done	Surgical debulking, delayed chemotherapy until symptomatic. C/E then VDC	Died at 42 months
8	26	Bilateral (solid)	745.8	Negative	Surgical debulking, P6 chemotherapy	Died at 23 months
9	19	Bilateral (solid)	2823	Supports	Surgical debulking, BEP	Died at 11 months
10 (Fang et al., 2008)	13	Left: 10 cm	Not done	Inconclusive	Surgical debulking, BEP, radiotherapy	Died at 21 months
11 (Fang et al., 2008)	23	Right: 11 cm Left: 9 cm	51.7		Surgical debulking, myeloablative chemotherapy	Alive at 7 months
12 (Engohan-Aloghe et al., 2009)	21	Right: 18 cm (solid) Left: unclear (solid)	Not done	Supports	Surgical debulking, unknown chemotherapy	Alive at 7 months
Case 1	6	Bilateral (solid)	Not done	Supports	Surgical debulking, P6 chemotherapy	Died at 28 months
Case 2	28	Right: 10 cm (solid/cystic)	42	Negative	Neoadjuvant IE/VDC chemotherapy, debulking surgery	Died at 40 months
Case 3	17	Right: 15 cm (multicystic)	35.9	Supports	Surgical debulking, IE/VDC chemotherapy with interval debulking followed by radiation therapy	Alive at 11 months

Summary of reported cases of ovarian DSRCT (modified from Ota et al., 2010) BEP: bleomycin, etoposide, and cisplatin; C/E: cisplatin, etoposide; VDC: vincristine, adriamycin, and cyclophosphamide; IE: ifosfamide, etoposide.

ifosfamide and etoposide (IE) between each VDC cycle for a total of seven cycles, is often used. Unfortunately, the efficacy of the high dose alkylator regimens comes with significant toxicity requiring support with transfusions and antibiotics (Kushner et al., 1996).

The three patients in our series have consistent presentations, response to treatment and survival to that seen in previously reported cases. Given the rarity of this clinical entity, ovarian DSRCT is unlikely to be on the differential diagnosis for an adnexal mass, but one should keep it in mind in young patients with peritoneal metastasis. Although maximal tumor debulking is preferred, its efficacy in improving survival is not as clear in ovarian DSRCT as it is for epithelial ovarian cancer and quality of life issues must be taken into account when determining course of therapy (Church et al., 2006). Therefore, foregoing radical surgery and the attendant morbidity may sometimes be a better option to avoid delaying initiation of chemotherapy. Despite aggressive therapy, patients with ovarian DSRCT face a poor prognosis which highlights the need for further research and improved therapeutic options.

Conflict of interest statement

We have 4 authors who each fulfill the requirements for authorship and there are no conflicts of interest or financial support to report.

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