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Case Report .

Ovarian Desmoplastic Small Round Cell Tumor: A Case Report of a Rare Devastating Cancer

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ABSTRACT

Desmoplastric small round cell tumor (DSRCT) is a rare highly malignant tumor, which was first described, by Gerald and Rosai in 1989 with predominance in male adolescence. However, a case series review showed early age incidence in females with median age of 14 years old. Majority of DSRCT patients present late. Due to rarity of this disease entity, ovarian DSRCT is unlikely to be on the differential diagnosis for an ovarian mass. We report a rare devastating malignant disease in unusual site of a young adolescent girl, initially responded to few cycles of chemotherapy.

Keywords: Ovarian Desmoplastic Tumor; Ifosfamide-Related Encephalopathy; Secondary Amenorrhea.

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INTRODUCTION

Desmoplastic small round cell tumor (DSRCT) is a rare, aggressive small round cell neoplasm derived from multipotent differentiated primitive cells able to express mesenchymal, epithelial, and neural markers. It was first described by Gerald and Rosai in 1989[1], and then formally named in 1991 in a case series of 19 patients affected by small round cell tumors with a consistent clinical and immunophenotypical presentation.[2] It commonly causes multiple masses in the intra-abdominal and pelvic cavities, and is more common in males. DSRCT is characterized by fusion of the N-terminal domain of the *Ewing sarcoma* gene (*EWSR1*) to the C-terminal domain of the *Wilms' tumor suppressor* gene (*WT1*) to yield the *EWSR1–WT1* fusion gene. This process is initiated by recurrent t(11;22)(p13;q12) translocation, which causes the generation of a chimeric protein with transcriptional regulatory activity.[3] DSRCT is best diagnosed by pathologic examination: typical findings include nests of uniform small round or splendid cells of variable size within a prominent fibroblastic stroma, and a poly-immunophenotype comprising multipotent differentiated primitive mesenchymal cells or neuroectodermal and primitive mesenchymal tissue.[4] A retrospective cohort analysis of 192 patients treated between 1973 and 2007 from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (Rockville, MD, USA) reported an incidence of DSRCT of 0.3 cases/million, with the primary site in the soft tissues of the abdomen and pelvis and, less commonly, the ovaries (six patients) and neurologic tissue (three patients).[5] The prognosis of DSRCT has remained poor since the first case report because there is no standard treatment approach. The 3-year survival rate of DSRCT is estimated to be 29%, whereas the 5-year survival rate is estimated to be 18%.[6,7] In addition, 71% of patients out of 39 cases described in one study died within a mean of 25.5 months.[8]

CASE PRESENTATION

A 12-year-old girl was admitted for the evaluation of abdominal and back pain with abdominal distention that had progressed over the preceding 2 months. The patient had experienced secondary amenorrhea for the preceding 4 months and decreased appetite for the preceding 2 months.

She was the product of full-term spontaneous vaginal delivery at home without complications, and had no previous medical or surgical issues. A physical examination revealed a large pelvic/abdominal mass with irregular margins and tenderness. Initial ultrasonography revealed a huge heterogeneous mass

measuring approximately 18 × 10 × 8.7 cm occupying the pelvis and lower abdomen and obscuring the view of both ovaries. Free fluid was visible in the abdomen and pelvis. Mildly increased echogenicity of both kidneys was identified with bilateral hydronephrosis more prominent on the left side, where the maximal renal pelvis measurement was 1 cm. Computed tomography (CT) scanning showed an abdominopelvic mass measuring approximately 10.5 × 9 × 15 cm with peritoneal deposits that was probably ovarian in origin (Figure 1). The mass was inseparable from the bladder and rectum, and was proposed to be a germ cell tumor. In addition, the CT scan revealed bilateral moderate hydronephrosis and compression of the left common iliac vein by the mass. Moreover, the CT scan identified an enlarged left supraclavicular lymph node, measuring approximately 2 × 1.2 cm. Work-up staging revealed only locally advanced cancer.

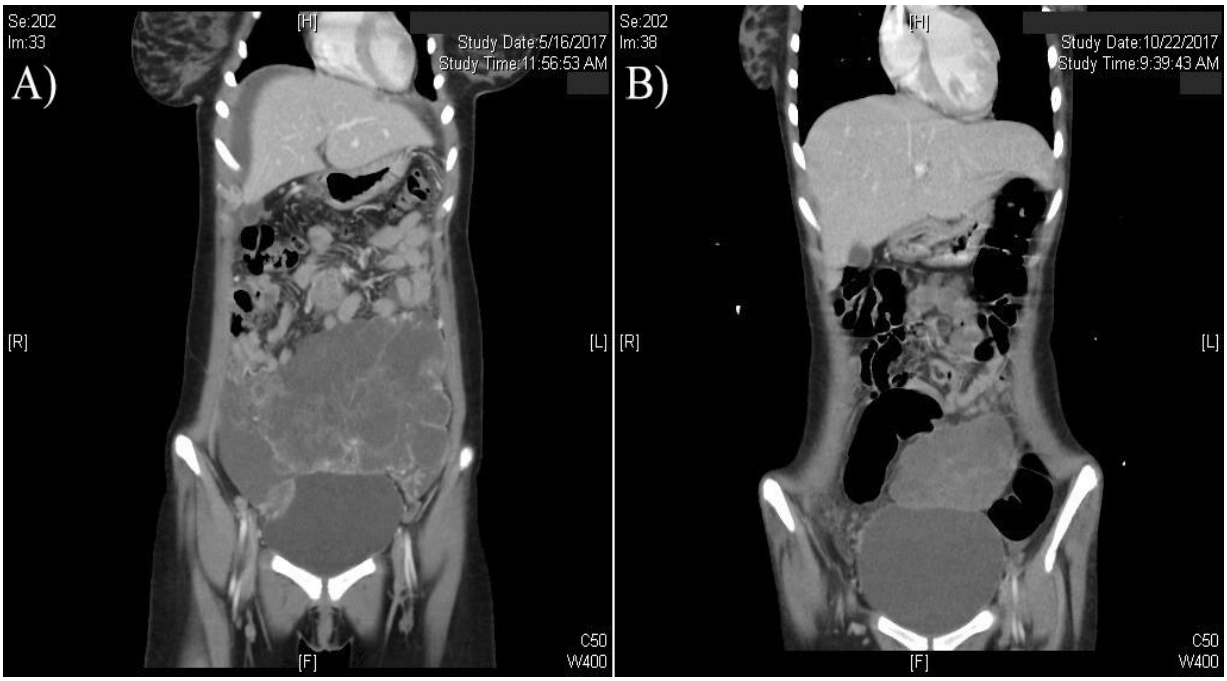

Figure 1. Coronal CT scan of pre and post chemotherapy in DSRCT. Left image (A) shows abdominopelvic mass 10.5 x 9 x 15 cm with peritoneal deposits and probably ovarian in origin. After eight cycles of chemotherapy, the mass was reduced in size significantly in the right image (B). That mass was inseparable from bladder and rectum in addition to bilateral moderate hydronephrosis and left common iliac vein compression.

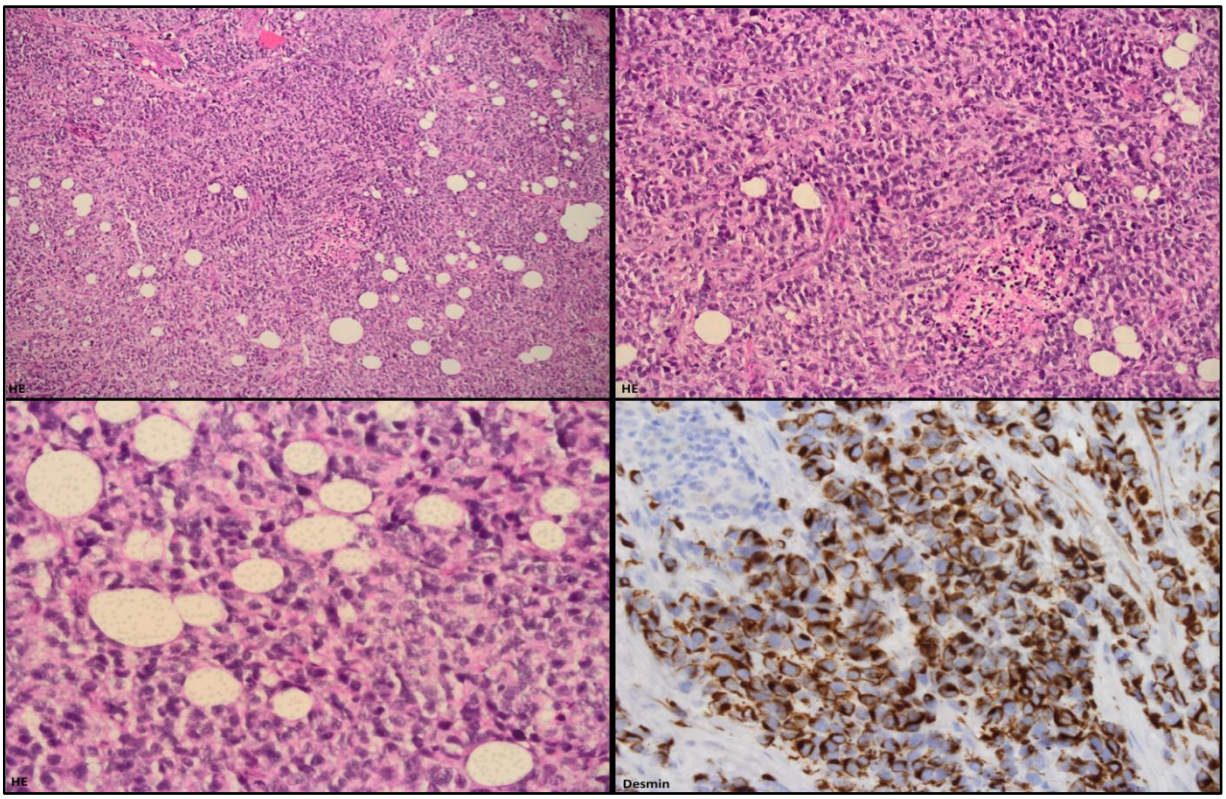

Figure 2. Hematoxylin and Eosin (HE) stain shows infiltrating nests, cords of round blue tumor cells with vesicular hyperchromatic irregular nuclei, and a surrounding desmoplastic reaction. Immunohistochemistry shows positive Desmin.

An incisional biopsy of the mass and an omental biopsy were taken during an exploratory laparotomy. The abdominopelvic mass showed bilateral ovarian tumors with peritoneal deposits and lymphadenopathy, indicating locally advanced ovarian tumor. There were multiple peritoneal seeding masses; the unresectable mass was huge, nodular, and firm-to-hard in consistency; and it occupied the whole pelvic cavity, extending above the level of the umbilicus.

Microscopy revealed fibrous tissue with infiltrating nests, cords of round blue tumor cells with vesicular hyperchromatic irregular nuclei, and a surrounding desmoplastic reaction (Figure 2).

The neoplastic cells were strongly positive for membranous Cluster of differentiation (CD) 99, focally positive for Cytokeratin AE1/AE3, multifocally strongly positive for epithelial membrane antigen, positive for cytoplasmic and punctate Desmin expression, and positive for WT1 (but negative for nuclear WT1) (Figure 3). The cells were also strongly positive for Vimentin. The cells were negative for CD45, Tdt, myogenin, MyoD1, S100, NSA, Synaptophysin, CD30, PLAP, ER, PR, CD117, CK7, CK20, CD34, and inhibin. Bone scanning showed that the right kidney had a dilated collecting system, whereas the left kidney appeared enlarged and lobulated with increased uptake and was suspicious for obstruction. Otherwise, no significant focal bony abnormalities were demonstrated, and no metastatic bone disease. Bone marrow aspiration was negative.

Initially, the patient received eight cycles of multi-agent chemotherapy as per the Children's Oncology Group (COG) protocol (Vincristine, Ifosfamide 3 grams/m^2/day for 3 days, Doxorubicin 20 mg/m^2/day for 2 days, and Etoposide 150 mg/m2/d for 3 days, and Actinomycin 0.75 mg/m^2/d for 2 days). On second day of Ifosfamide infusion, her mental status worsened from drowsiness to stupor followed by disorientation and emotional changes.

Her blood test results, including measurements of serum glucose, and electrolytes, were normal, and brain magnetic resonance imaging (MRI) findings were normal. She was diagnosed with Ifosfamide-induced encephalopathy, and her chemotherapy was immediately discontinued. She received Methelyene blue 50 mg IV every 4 hours until recovery. After 48 hours, her neurological status completely recovered without any residuals. Then Ifosfamide chemotherapy containing course was later substituted with Cyclophosphamide.

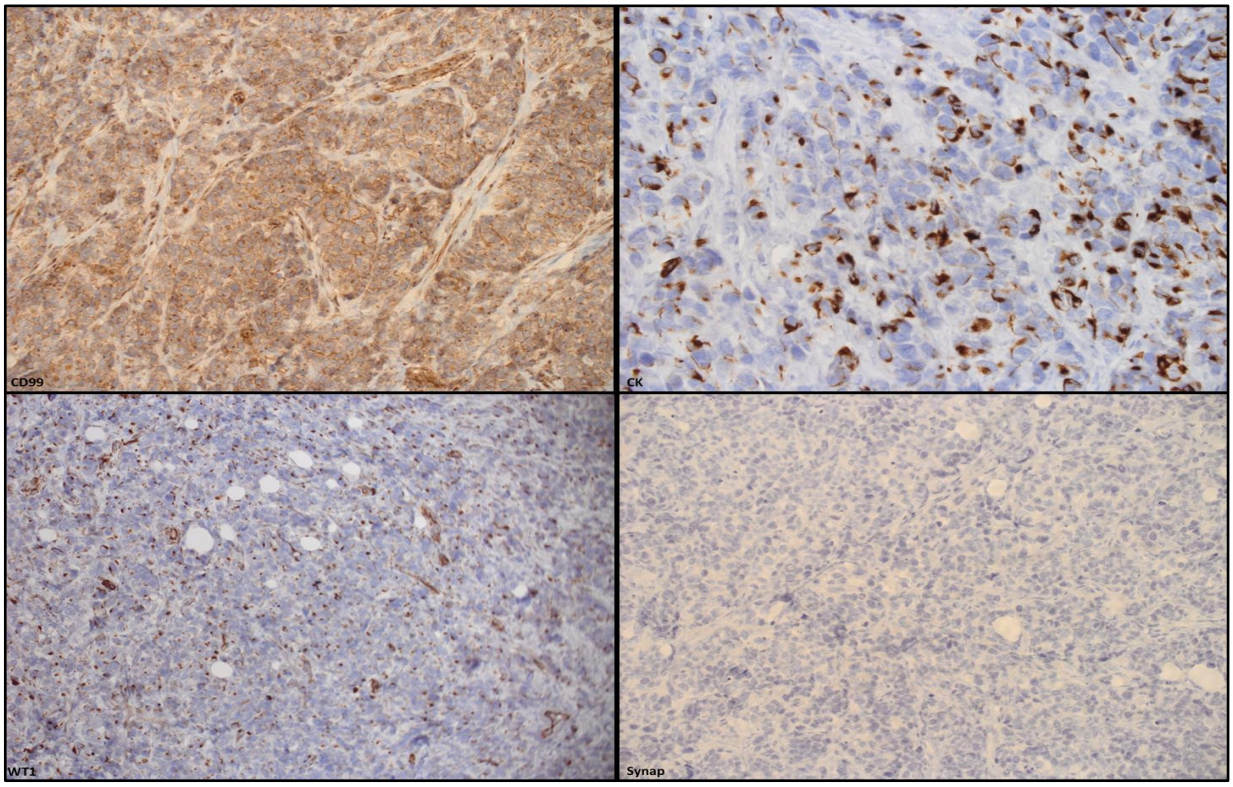

Figure 3. Immunohistochemistry showed membranous CD99 and CK dot positivity. WT1 and Synaptophysin were both negative.

DISCUSSION

First described by Gerald and Rosai in 1989[1], DSRCT is a rare and aggressive tumor that predominantly arises in adolescence. It is pathognomonic of the t(11;22)(p13;q12) translocation, which results in the formation of an *EWSR1–WT1* fusion protein that possesses transcriptional regulatory activity.

Several studies have described the male predominance of DSRCT, which has a median age at diagnosis of 19 years and reported male:female ratios of 5:1 and 10:1.[2,9] However, a review of 17 cases concluded that DSRCT can occur earlier in females than in males, with a median age at diagnosis of 14 years, and that it can involve the ovaries more often than described in the literature.[10,11] Data from the SEER Program of the National Cancer Institute showed that the age-adjusted incidence of DSRCT is 0.3 cases/million in patients aged 20–24 years.[5] Furthermore, the SEER data demonstrated no differences in 5-year survival rates between males and females or between patients aged less than 18 years compared with older patients.[5] Generally, only one ovary is involved; however, the discovery of widespread metastatic disease throughout the peritoneal cavity on presentation is common. The most commonly involved sites are the lymph nodes, liver, and lungs.[5,12,13]

The signs and symptoms of DSRCT include abdominal distention with a palpable mass, abdominal pain and tenderness, secondary amenorrhea or testicular swelling, constipation and intestinal obstruction, and other mass effect signs and symptoms. The index patient presented with a history of progressive abdominal distention, an apparent mass with an irregular margin, lack of mobility, and undefined boundaries, and tenderness on palpation. In addition, the patient complained of secondary amenorrhea due to involvement of the tumor in both ovaries. These symptoms and signs are not specific, and may worsen the tumor burden at the time of diagnosis, overwhelming the organs involved with metastases. Patients rarely raise clinical suspicion of or are diagnosed with DSRCT at an early stage. However, the possibility remains of finding DSRCT masses incidentally during other surgical procedures, such as hernia repair or exploratory abdominal surgery for other reasons.[14]

There is no validated staging system for DSRCT, yet many patients are proposed to have Stage IV disease at diagnosis. A small cohort study that included 24 patients proposed a new staging system based on criteria related to tumor burden according to the Peritoneal Cancer Index (PCI) of Harmon and Sugarbaker for liver and extra-abdominal metastases.[15,16] Stage I is a PCI score of <12 without liver and extra-abdominal metastases. Stage II is a PCI score of >12 without liver and extra-abdominal metastasis. Stage III is any PCI level with liver metastases but no extra-abdominal involvement. Stage IV is any PCI level with liver and extra-abdominal metastases. However, this staging system did not establish statistical significance because of the small number of patients involved.

The diagnosis of DSRCT remains challenging, and clinical suspicion is rare in the early stages. Pathologic, immunohistochemical, and cytogenetic tests are the mainstays of establishing the diagnosis. Most patients with DSRCT have consistent histopathologic findings of fibrous tissue featuring infiltrating nests, cords of atypical round blue tumor cells with vesicular hyperchromatic irregular nuclei, and a surrounding desmoplastic reaction. The infiltrating nests express mesenchymal (Vimentin and Desmin), epithelial (Cytokeratin), and neural markers.

Imaging studies are useful in assessing and staging the extent of DRSCT, yet they cannot show the characteristic features of the tumor. CT is the most useful imaging modality for the assessment of multiple masses and metastasis associated with DRSCT involving the peritoneum, whereas magnetic resonance imaging is suitable for the assessment of pelvic and hepatic metastases.[17] A retrospective study involving 65 patients in which the efficacy of functional positron emission tomography/CT with fluorodeoxyglucose for diagnosing DRSCT was reviewed demonstrated the superiority of the technique over anatomic imaging, with an accurate detection rate of 97.4% of all DSRCT lesions.[17] The study concluded that the common radiologic findings were dominant masses in the retrovesical or rectouterine pouches, with peritoneal soft tissue masses and common metastases in the liver, lungs, spleen, and bones.[17] Our patient exhibited a dominant abdominopelvic mass of probable ovarian origin that was inseparable from the bladder and rectum and featured peritoneal deposits. Moreover, the mass was causing compressive bilateral moderate hydronephrosis and compression of the left common iliac vein.

A multimodal chemotherapeutic approach to DSRCT has been used since 1989, and includes intensive alkylator-based therapy, debulking surgery, radiotherapy, hyperthermic intraperitoneal therapy (HIPEC), and autologous stem-cell rescue. A highly aggressive regimen is commonly used to treat DRSCT, which involves seven courses of chemotherapy using the Memorial Sloan Kettering Cancer Center P6 Regimen. The first to third and sixth courses include cyclophosphamide or ifosfamide, and vincristine and doxorubicin alternate in the fourth, fifth, and seventh courses with ifosfamide and etoposide.[7] In a study by Kushner et al. in which this regimen was used, seven of 12 patients experienced complete remission for 32 months. However, this survival duration was not experienced by a patient suffering from DSRCT with primary ovarian involvement, which recurred in 11 months.[11] Another therapeutic option shown to be safer in pediatric patients than in adults is the use of HIPEC after cytoreductive surgical removal of the tumor.[16] Pediatric patients who received HIPEC showed an increase in median 3-year survival time of 8.85 months (71%) compared with the mean survival, although this was not statistically significant. Our patient received eight cycles of multi-agent chemotherapy as per the COG protocol. Initially, she received ifosfamide, but this was later replaced with cyclophosphamide following the development of temporal ifosfamide-related encephalopathy. Her initial symptoms disappear, and her quality of life is currently much better.

CONCLUSION

DSRCT is a rare, highly aggressive malignant tumor that affects adolescents and in particular young men. The majority of patients with the condition present with advanced disease. Because of the rarity of this entity, ovarian DSRCT is unlikely to be considered during the differential diagnosis of an ovarian mass, but it should be kept in mind during the evaluation of young patients with recurrent abdominal pain, abdominal distension, and peritoneal metastasis. A combination of surgery, chemotherapy, and radiotherapy is often used to treat DRSCT; however, it is difficult to confirm whether surgery before or after chemotherapy is most effective in patients with the disease. This highlights the need to consider DRSCT during the differential diagnosis of gynecologic malignancies. Regardless of the intensive therapeutic options described in many studies, patients with DRSCT face a poor prognosis and a high recurrence rate. Further extensive studies and randomized controlled trials are necessary to establish a standardized staging system for more effective treatment of this devastating condition.

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