

Paratesticular Desmoplastic Small Round Cell Tumors: A Case Report and Review of the Literature

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Brief running title: Paratesticular DSRCT Case Report and Review

Abbreviations

DSCRT	Desmoplastic Small Round Cell Tumor
EMA	Epithelial Membrane Antigen
SEER	Surveillance, Epidemiology and End Results
NSE	Neuron Specific Enolase
COG	Children's Oncology Group

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WES

Whole Exome Sequencing

CT

Computerized Tomography

PET

Positron Emission Tomography

Abstract

Desmoplastic small round cell tumor is a rare malignancy most often seen in the abdomen or pelvis of young men. Unfortunately, this disease is usually metastatic at diagnosis and has dismal outcomes. It appears that isolated, paratesticular desmoplastic small round cell tumors have a markedly better outcome than the classic abdominal or pelvic location. We hypothesize this is due to earlier detection and the relative ease of surgical resection. We review the literature and describe a case of isolated paratesticular desmoplastic small round cell tumor in a 14-year-old male successfully treated with surgical resection, chemotherapy and adjuvant radiation.

Key Words

paratesticular, desmoplastic small round cell tumor, surgical resection, chemotherapy

Introduction

Desmoplastic small round cell tumor (DSRCT) is a rare, aggressive malignancy initially described by Gerald and Rosai in 1989 and most often seen in adolescent and young adult patients^{1,2}. Histologically, it consists of small round blue cells with a desmoplastic reaction. The immunohistochemical profile demonstrates reactivity for cytokeratin, EMA, vimentin and desmin¹. Fusion of the EWSR1 and WT1 genes is diagnostic for DSRCT².

Patients with DSRCT are usually between 5 and 30 years of age. Males and older adolescents are more often affected^{2,3}. A review of pediatric SEER data found 95 reported cases in patients 0-21 years of age between 1991 and 2011³.

DSRCT is most frequently found on abdominal or pelvic serosal surfaces though many other locations are reported⁴. The abdominal or pelvic location can allow the tumor to grow for some time before causing symptoms. When symptoms are present, they are generally vague such as weight loss, abdominal fullness and abdominal pain. Therefore, DSRCT is often not diagnosed until the disease burden is large and/or there is metastatic disease. In the SEER database, only 20% of patients had localized disease at presentation³.

The outcomes for DSRCT are quite poor with only 15-30% overall survival at 5 years^{2,3}. A multi-modal approach to DSRCT therapy is recommended, especially for metastatic disease. Treatment is not standardized but generally includes local control with surgical resection and/or radiation along with multiagent chemotherapy^{2,5}. There are reports of hyperthermic intraperitoneal radiation and high dose chemotherapy followed by autologous stem cell transplant but neither therapy has demonstrated a definitive survival

benefit^{2,5-7}. We present a case of a successfully treated isolated paratesticular DSRCT and review the literature.

Case Description

Our patient was a healthy 14-year-old male when he presented to the pediatric surgery clinic with an approximately 1 month history of a left groin bulge. He had no complaints of fevers, weight loss or pain. He was diagnosed with an apparent inguinal hernia and scheduled for surgical repair. In the operating room, he was discovered to have a multi-lobulated paratesticular mass. Frozen section revealed a small round blue cell tumor and he underwent gross total resection of the mass with left orchiectomy.

Pathology showed a malignant small round blue cell tumor with islands of poorly differentiated cells, areas of necrosis and areas of brisk mitotic activity. The tumor was diffusely positive for NSE and desmin with focally positivity for EMA and pancytokeratin. Myogenin, CD99, CD3, CD45, CD20 and inhibin were all negative. INI-1 was retained. Further molecular testing by PCR demonstrated EWSR1/WT1 chimerism; diagnostic of DSRCT. Cytogenetics demonstrated a gain of chromosome 5, also consistent with DSRCT. His testis was negative for disease.

Our patient was enrolled on a prospective integrative clinical sequencing trial (PEDS-MIONCOSEQ) and underwent paired tumor/normal whole exome sequencing (WES) and tumor transcriptome sequencing (RNA-Seq). Specifics of the sequencing procedure and bioinformatics analysis have been previously described⁸. The study detected the characteristic EWSR1-WT1 gene fusion, copy gains in of chr1q, 3, 5, 9, 15 and 21, as well as a somatic mutation of MAP3K13 at a low allelic frequency of 5.7%; the significance of which

remains unknown in this tumor⁹. Our patient had microscopic positivity at the tumor margins and the remainder of his staging evaluation including abdominal/pelvic laparoscopic exploration, CT chest/abdomen/pelvis and PET scan was negative.

Our patient was then treated with chemotherapy and adjuvant radiation. His chemotherapy was in accordance with Children's Oncology Group (COG) protocol AEWS1031 arm B with vincristine, topotecan, cyclophosphamide, doxorubicin, etoposide and ifosfamide. He received 50.4 Gray of adjuvant radiation to the tumor bed after cycle 6 of chemotherapy due to his microscopically positive margins. He tolerated radiation and all 17 cycles of chemotherapy without any significant side effects. At the time of manuscript submission he is 24 months from diagnosis and 13 months from completion of chemotherapy without evidence of disease.

Discussion

Paratesticular DSRCT is rare with only 20 such cases reported in the literature. (Review limited to literature with at least an abstract available in English). Like DSRCT in general, it is seen in older adolescents and young adults. The youngest patient previously reported in the literature was 17. Our patient was 14 at the time of diagnosis.

Paratesticular DSRCT can present with an isolated mass or with metastatic disease. Of the 20 reported cases, 12 had localized disease (see Table 1)^{4,5,10-16} and 8 had metastatic disease at the time of diagnosis (see Table 2)^{10,17-21}. Most patients presented due to a mass or testicular pain. Our patient presented with a painless mass and his staging evaluation did not find any metastatic disease.

There is no standardized treatment approach for DSRCT but surgery is the preferred means of local control². All of the reported paratesticular DSRCT patients underwent surgical resection, often with orchiectomy. The ubiquity of surgery is likely because the paratesticular location makes surgery feasible sooner after diagnosis and less morbid. Our patient underwent a gross total excision with high inguinal orchiectomy.

Radiation therapy is also commonly used for local control in DSRCT, especially for those unable to undergo surgical resection². The dose and field of radiation administered varies^{2,4,5}. Interestingly, none of the reported patients with paratesticular DSRCT received radiation therapy. We opted to give our patient adjuvant local radiation therapy due to his microscopically positive margins. In our review, the post-surgical margin status was not addressed for any of the cases.

Multiagent chemotherapy is considered standard therapy for DSRCT in the neoadjuvant or adjuvant setting. A variety of chemotherapy regimens have been used and most are similar to approaches used for Ewing sarcoma². Based on the limited literature for DSRCT treatment, we chose the most recent pediatric Ewing protocol, the COG protocol AEWS1031.

Despite multimodal therapy, patients with DSRCT overall have very poor survival rates of 15-30% at 5 years^{2,3}. Patients with paratesticular DSRCT appear to have far better outcomes. Out of the 20 previously reported cases of paratesticular DSRCT, 17 had follow up data available. Of those 17, 10 (~60%) were alive without evidence of disease between 6 and 120 months off therapy. When only patients with metastatic disease are considered, 2 of 6 (33%) were alive 6 to 30 months after diagnosis. However, for those patients with isolated

paratesticular disease, 8 of 10 (80%) were alive without evidence of disease 33 to 120 months after diagnosis. One patient was alive with disease 12 months after diagnosis. This review suggests that the survival rate for isolated paratesticular disease is better than metastatic paratesticular disease and the outcomes in paratesticular location in general are much better than the DSRCT outcomes overall. Accordingly, our patient is alive and well without evidence of disease 24 months after diagnosis.

The dramatically improved survival of isolated paratesticular DSRCT compared to DSRCT overall is likely due to its location. The location of the mass renders itself to early detection by patients which leads to earlier medical intervention. The paratesticular location also improves the feasibility of complete surgical excision.

It is unclear if paratesticular DSRCT tumors are biologically distinct from the more typical, widely metastatic DSRCT. While the tumor sequencing did not show any actionable targets in our case, ongoing studies will hopefully identify novel targeted therapies that are less toxic and more effective for this disease.

Conflict of Interest Statement

No author has a conflict of interest.

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TABLE 1 Isolated Paratesticular Desmoplastic Small Round Cell Tumors Reported in the Literature

First Author	Number of Patients ¹	Patient Age (Years)	Treatment	Patient Outcome at Time of Report
<i>Bisogna</i>	1	17	Complete surgical resection with orchiectomy, chemotherapy (VCR, D, I)	NED 63 months after diagnosis
<i>Cummings</i>	4	17	Orchiectomy ² , chemotherapy (CDDP, D, CPM)	Lost to follow up
		28	Orchiectomy ² chemotherapy ³	Relapse in cervical lymph nodes at 7 months after diagnosis, DOD 16 months after diagnosis
		28	Orchiectomy ² , chemotherapy ³	Relapse with pulmonary disease at 24 months after diagnosis, NED at 36 months after diagnosis
		37	Orchiectomy ²	Relapse in the retroperitoneum 36 months after diagnosis, lost to follow up
<i>Farhat</i>	1	?	Orchiectomy ² , chemotherapy (CDDP, Epi, CPM, VP16)	NED 32 months after relapse (unclear if metastatic disease at diagnosis, widespread disease at relapse)
<i>Furman</i>	1	21	Surgical resection ² , chemotherapy (Carbo, I, VP16, VCR, CPM, A)	NED 33 months after diagnosis
<i>Garcia-Gonzalez</i>	1	23	Surgical resection ² , chemotherapy (Initial: MTX, Dacarb, CPM, D, VCR; Subsequent: D, VCR, A, CPM)	NED 72 months after diagnosis
<i>Ordonez</i>	1	28	Orchiectomy ² , chemotherapy (CDDP, VP16)	AWD: regional metastatic disease 12 months after diagnosis (unclear if metastatic

				disease at diagnosis)
<i>Roganovich</i>	1	17	Complete surgical resection, chemotherapy (I, D, VCR)	NED 60 months years from diagnosis
<i>Saab</i>	1	19	Complete surgical resection, chemotherapy (Carbo, VCR, A, CPM, I, VP-16)	NED at 120 months from diagnosis
<i>Sha</i>	1	27	Orchiectomy ² , chemotherapy (CDDP, VP16, I, Epi)	NED 36 months from diagnosis

NED = no evidence of disease DOD = dead of disease AWD = alive with disease A = doxorubicin Carbo = carboplatin

CDDP = cisplatin CPM = cyclophosphamide D = dactinomycin Dacarb = dacarbazine Epi = epirubicin I = ifosfamide MTX = methotrexate VCR = vincristine VP16 = etoposide ¹only newly reported patients are included ²unclear if complete surgical resection ³unclear which chemotherapy used and if it was given up front, at relapse or both

TABLE 2 Metastatic Paratesticular Desmoplastic Small Round Cell Tumors Reported in the Literature

First Author	Number of Patients ¹	Patient Age (Years)	Location of Metastasis (at diagnosis)	Treatment	Patient Outcome at Time of Report
<i>Cliteur</i>	1	32	Abdomen	Orchiectomy, chemotherapy (VCR, VP16, I, A)	DOD 24 months after diagnosis
<i>Cummings</i>	2	32	Retroperitoneal mass	Orchiectomy	Lost to follow up
		26	Lungs, lymph nodes	Orchiectomy, chemotherapy ² , bone marrow transplant	NED 30 months after diagnosis
<i>Prat</i>	1	22	Lungs, lymph nodes (regional and distant)	Orchiectomy, chemotherapy ²	DOD 17 months after diagnosis
<i>Rais</i>	1	27	Abdomen	Surgical resection, chemotherapy ²	NED 6 months after diagnosis
<i>Thuret</i>	1	34	Retroperitoneal	Orchiectomy, chemotherapy ²	?
<i>Yue</i>	2	25 and 35	Abdominal and retroperitoneal	One received orchiectomy, hepatic artery embolization, and chemotherapy (CPM, Pir, Vind, Dacarb), the other received chemotherapy alone (CPM, Epi, Vinp) (unclear which patient received surgery)	Unclear but appears they both are DOD

NED = no evidence of disease DOD = dead of disease AWD = alive with disease A = doxorubicin CDDP = cisplatin

CPM = cyclophosphamide Dacarb = dacarbazine Epi = epirubicin I = ifosfamide Pir = pirarubicin VCR = vincristine Vind = vindesine

Vinp = vinpocetine VP16 = etoposide ¹only newly reported patients are included ²unclear which chemotherapy used

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