A testicular and paratesticular localization of Desmoplastic Small Round Cell Tumor: Is it a good prognostic factor?

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Abstract

Desmoplastic Small Round Cell Tumor (DSRCT) is an aggressive neoplasm that classically grows in peritoneal cavity and has poor prognosis. We describe a 13-year old boy with testicular DSRCT, treated with orchiectomy and chemotherapy and is free of disease 96 months after diagnosis. This is the fifth case of primary DSRCT of the testis described in literature. Moreover, we present a literature review of 28 cases of testicular and paratesticular DSRCT and discuss these locations as a prognostic factor.

Introduction

Desmoplastic Small Round Cell Tumor (DSRCT) is a rare neoplasm that affects mainly adolescent and young adult males. This tumor presents with a polyphenotypic differentiation profile, showing muscular, neural and epithelial markers and carries the recurrent chromosomal translocation t(11;22)(p13;q12)[1,2] . Abdomen/pelvis are the major sites of growth and the prognosis is poor, but data from literature shows that patients with paratesticular DSRCT have better outcomes[2-4] . We present the fifth case of primary DSRCT of the testis described in literature and discuss these locations as a prognostic factor.

Case Description

A 13-year-old boy presented with a 9-month history of right testicle swelling. Ultrasound and magnetic resonance imaging of the scrotum revealed a 1.7 x 1.4 cm solid nodule in the right testis **(Figure 1)** and he underwent a right radical orchiectomy. Histopathological exam showed a whitish neoplastic proliferation in testicular tissue, measuring 1.9 x 1.8 cm, with trabecular arrangements interspersed with fibrous tissue and covered by small, round and blue cells, with few enlarged nuclei and scarce cytoplasm. The nodular tumor was confined to the testis and evaluation of spermatic cord was normal. Immunohistochemistry revealed diffuse positivity for cytokeratin AE1/AE3, neuron-specific enolase and desmin in dot-like pattern. There was also focal positivity for EMA. Chromogranin, synaptophysin, myogenin, inhibin and muscle-actin-specific HHF-35 were negative; INI-1 was intact. Ki-67 proliferation index was 20%. Morphological and immunohistochemical findings were compatible with DSRCT. After diagnosis, the patient was referred for our hospital. Complementary staging exams did not show distant metastases. Next-Generation Sequencing by Illumina NextSeq 500 System was performed, and EWS-WT1 fusion gene was positive, confirming the diagnosis of DSRCT. We then started adjuvant chemotherapy, consisting of 10 cycles of Irinotecan (50mg/m^2/d, day 1 to 5) and Vincristine (1.5mg/m^2/d, day 1 and day 7). No radiation therapy was performed. Currently the patient is disease-free 96 months after diagnosis.

Discussion

DSRCT is an aggressive tumor that develops in serous cavities, mainly in the abdomen/pelvis, and spreads generating multiple peritoneal implants. The age-adjusted incidence rate of DSRCT is 0,3 cases/million, with a peak incidence of 0,74 cases/million in those aged 20-24 years[5] . In a series of 60 patients, 93% had intra-abdominal tumor and 90% had metastases at diagnosis[6] . Extra-abdominal DSRCT is rare, affecting about 5-27% of cases and was reported in several sites, like parotid glands, pleura, tibia and the paratesticular region[4,7-9] .

Although paratesticular DSRCT has been reported since 1992, primary DSRCT of the testis was first described by He and colleagues in 2013[10] . In our literature review we found 23 cases of paratesticular and 5 of testicular tumors, including the case here reported **(Table 1)** . Of the 5 testicular DSRCT, 2 cases presented with extension to the epididymis/spermatic cord and in another case the tumor invaded rete testis with infiltration to lymphovascular spaces[10-12] . Of the paratesticular tumors, not one infiltrated the testis. In contrast, testicular DSRCT seems to invade paratesticular regions. The present case report is the fifth testicular DSRCT in the literature.

Translocation t(11;22)(p13;q12) is the hallmark of DSRCT and the fusion occurs in exon 7 of EWS gene and exon 8 of WT1 gene[2,13,14] . This fusion results in a chimeric protein capable of acting as a transcription factor in more than 30 genes, such as the growth factor genes PDGF, EGFR and IGF-1[15,16] . Although the EWS-WT1 transcript is characteristic of DSRCT, it is still not known if the fusion is specific to this disease. Alaggio et al described 2 cases of intra-abdominal leiomyosarcomas positive for the EWS-WT1 fusion in children 9 and 11 years old. One of the cases presented as a single abdominal mass and both had a favorable course[17] . Two cases that we reviewed presented unusual fusion with EWS in exon 9 and WT1 in exon 8, one a paratesticular DSRCT and the other testicular[12,14] . Al-Ibraheemi described a series of 16 cases with DSCRT with atypical location; all of them presented the typical EWS-WT1 fusion, demonstrating that the molecular signature of DSRCT in atypical sites seems to be the same as of those in the abdomen, despite better outcomes[18] .

Patients with abdominal DSRCT are usually diagnosed with advanced disease and have poor prognosis, with overall survival ranging from 12 to 33% in 5 years, even with multimodal treatment. Resectable and non-metastatic tumors have better outcomes, regardless of their location[5,6,19,20] . Therefore, resectability is considered an independent prognostic factor. In a study by Wong et al, patients with non-metastatic, intra-abdominal disease at presentation who had undergone surgical resection of the primary tumor (n = 6) survived much longer than those who did not have surgery (n = 11), with median survival of 47 versus 16 months, respectively (p=0.0235)[21] .

Some studies suggest that patients with extra-abdominal tumors have better outcomes compared to the typical abdominal tumors[3,21] . Our review included 28 patients with testicular and paratesticular DSRCT. 6 of these were lost to follow-up. 12 out the remaining 22 (54%) were disease-free between 6 and 120 months after diagnosis. Differences of survival between testicular and paratesticular DSRCT was not significant due to the small number of cases and variable follow-up.

Survival improves considerably in non-metastatic testicular/paratesticular DSRCT. Of the 12 available patients, 9 were disease-free between 6-120 months after diagnosis and 3 died, resulting in a 75% disease-free survival.

In DSRCT with metastasis at diagnosis, regardless of testicular or para-testicular location, only 2 out of 8 cases were alive without evidence of disease 6 and 30 months after diagnosis. In our review, the most frequent sites of metastasis at the time of initial diagnosis or at the time of recurrence diagnosis were retroperitoneal lymph nodes (9 cases) and lungs (6 cases).

Resection surgery was possible in 93% of patients with paratesticular/testicular DSRCT, with orchiectomy reported in 23 of 28 cases, signaling the high resectability of these tumors when compared to abdominal DSRCT, in which less than 50% are completely resected[6,20] .

Currently, the most used chemotherapy regimen is based on alkylating agents, anthracyclines and vinca

alkaloids. However, several different regimens are reported in the literature[6,21] . Our patient was treated with Irinotecan. Some authors have shown that topoisomerase inhibitors, such as Irinotecan, can be effective in DSRCT[22-24] .

There is no consensus in the literature regarding the treatment of patients with DSRCT in the paratesticular or testicular regions due to the small number of cases. In non-metastatic cases the initial treatment is radical orchiectomy[3,4,12,25-28] , but in patients with disseminated tumors we cannot say that primary-tumor-surgery improves survival. The administration of chemotherapy seems to be consensual due to the potentially aggressive behavior of the tumor. However, at least in paratesticular or testicular disease, it appears that radiotherapy can be avoided in tumors that are completely resected, although further studies are needed for definitive conclusions. In metastatic tumors multimodal treatment is mandatory, and the prognosis is poor regardless of the primary tumor location.

Efforts are being made to discover targeted therapies in DSRCT, however there is currently no drug that has a target effect in the EWS-WT1 fusion. Several agents, especially tyrosine kinase inhibitors, such as pazopanib, imatinib and sorafenib are being studied[16] . A wide analysis of the genomic profile of DSRCT may provide data on whether other genetic alterations contribute to the growth and behavior of this tumor in different regions.

Ethical statement

Institutional Review Board approval was granted by the Federal University of Sao Paulo Research Ethics Committee, (reference no. 4.332.189) and the patient gave written informed consent for his de-identified clinical data to be published.

Conflict of interest statement

The authors declare that there is no conflict of interest. This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

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Figure legend: Preoperative magnetic resonance showing coronal and sagittal T2 SPAIR images of a primary testicular mass measuring 1.7x1.4 cm (arrow).

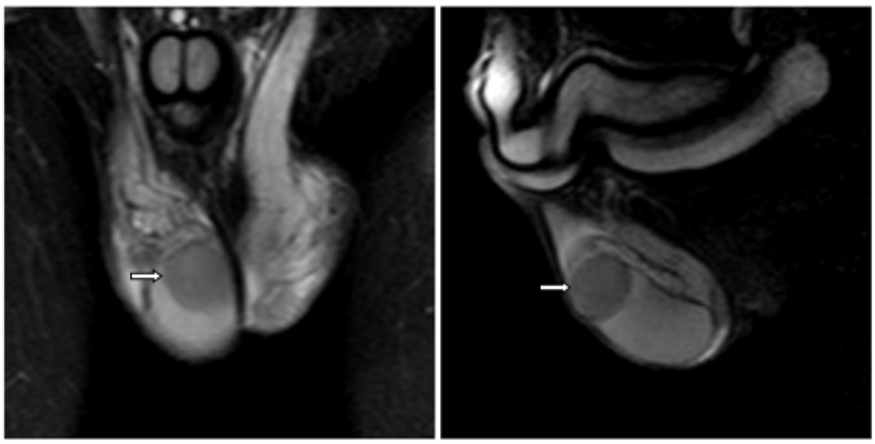

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Table 1.pdf available at https://authorea.com/users/366445/articles/486209-a-testicular-and-paratesticular-localization-of-desmoplastic-small-round-cell-tumor-is-it-a-good-prognostic-factor