Cytoredutive Surgery and Chemohyperthemia for Desmoplasic Small Round Cell Tumor in Pediatric Patient: Case Report

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Cirurgia Citorredutora e Quimioterapia Intraperitoneal Hipertérmica para Tratamento de Tumor Desmoplásico de Pequenas Células Redondas em Paciente Pediátrico: Relato de Caso

Cirugia de Citoreducción y Quimihipertermia el Tratamento de Tumor Desmoplásico de Pequeñas Células Redondas en Paciente Pediátrico: Relato de Caso

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Abstract
Introduction: Desmoplastic small round cell tumor (DSRCT) is rare and highly aggressive mesenchymal tumor. Objective: Case report of a 7 y-o boy, diagnosticated with a DSRCT, treated in the Pediatric Service at National Cancer Institute José Alencar Gomes da Silva. **Case report:** He presented with abdominal pain, abdominal mass, ascites, fever and slimming. Computer tomography showed a hypodense tumor on IV hepatic segment, volumous ascitis, tumoral mass in right hemithorax. He was submitted to needle biopsy with histopatologic result as DSRCT staged as IV. The patient was submitted to sistemic chemotherapy with complete response on thoracic tumor e abdominal tumor reduction, with stable pelvic lesions. An cytoredutive surgery with cisplatin hyperthermic intraperionteal chemotherapy. He received abdominal radiotherapy and chemotherapy. He presented with tumor progression and death after 14 months. **Conclusion:** Cytoredutive surgery and Hyperthermic intraperitoneal chemotherapy permitted a temporary disease control with a good quality of life.
Key words: Desmoplastic Small Round Cell Tumor; Children; Cytoreduction Surgical Procedures; Hyperthermia, Induced; Neoplasms.

Resumo
Introdução: O tumor desmoplásico de pequenas células redondas (TDPCR) é uma neoplasia rara com comportamento clínico agressivo. Trata-se do caso de um paciente com 7 anos de idade, sexo masculino, com TDPCR, matriculado no Serviço de Pediatria do Instituto Nacional de Câncer José Alencar Gomes da Silva. **Relato do caso:** Paciente iniciou o quadro com queixa de dor e aumento do abdome, ascite volumosa, febre e emagrecimento. Nos exames de imagem, apresentava lesão hipodensa no segmento IV A do fígado, ascite volumosa, massa justa parietal no hemitórax direito. O laudo histopatológico foi compatível com TDPCR estádio IV. O paciente foi submetido à quimioterapia sistêmica com resposta completa nas lesões torácicas e redução importante da massa abdominal, restando lesões em cavidade pélvica. O paciente foi submetido à cirurgia com citorredução e hipertermoquimioterapia com cisplatina, e recebeu radioterapia abdominal adjuvante e quimioterapia. O paciente manteve-se estável, apresentando nova progressão e óbito 14 meses após a recidiva. **Conclusão:** A citorredução cirúrgica associada à hipertermoquimioterapia intraperitoneal permitiu a possibilidade de controle temporário da doença com boa qualidade de vida para o paciente.
Palavras-chave: Tumor Desmoplásico de Células Pequenas Redondas; Crianças; Procedimentos Cirúrgicos de Citorredução; Hipertermia Induzida; Neoplasias.

Resumen
Introducción: El tumor desmoplásico de pequeñas células redondas (TDPCR) es una neoplasia rara con comportamento clínico agresivo. Objetivo: Relatar el caso de un paciente con 7 años de edad, sexo masculino con TDPCR, matriculado en el Servicio de Pediatria en el Instituto Nacional del Cancer José Alencar Gomes da Silva. **Relato del caso:** El paciente inició el cuadro con dolor y aumento del abdomen, ascite voluminosa, fiebre y adelgazamiento. En los exámenes de imagen presentaba lesión hipodensa en el segmento IV A del hígado, ascite voluminosa, masa justa parietal en hemitórax derecho. El histopatológico fue compatible con el TDPCR estadio IV. El paciente fue sometido a quimioterapia sistémica con respuesta completa en las lesiones toráxicas y reducción importante de la masa abdominal, restando lesiones en la cavidad pélvica. El paciente fue sometido a cirurgía con citorreducción e hipertermoquimioterapia con cisplatina. Recibió radioterapia abdominal adjuvante y quimioterapia. El paciente se mantuvo estable, presentando nueva progresión y óbito 14 meses después de la recidiva. **Conclusión:** La citoreducción cirúrgica asociada a la hipertermoquimioterapia intraperitoneal permitió la posibilidad de control temporario de la enfermedad con buena calidad de vida para el paciente.
Palabras clave: Tumor Desmoplásico de Células Pequenas Redondas; Crianças; Procedimentos Cirúrgicos de Citorredução; Hipertermia Induzida; Neoplasias.

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INTRODUCTION

Desmoplastic small round cell tumor (DSRCT) is a rare mesenchymal tumor[1,2]. The tumor belongs to the group of soft tissue sarcomas[1,3], with typical clinical, histological, and immunohistochemical characteristics[4]. Most DSRCT manifest as a large abdominal mass or scattered peritoneal foci and tend to display metastases at diagnosis (to lymph nodes, peritoneum, liver, lungs, and bones)[5-7]. The disease displays aggressive clinical behavior, tending to spread to the peritoneum as well as extraperitoneal sites, especially liver and lungs[5,8,9,10]. DSRCT is associated with the translocation t (11:22) (p13; q12), which involves the EWSRI and WT1 genes[6].

Despite multimodal treatment including aggressive surgical resection, chemotherapy, and radiotherapy, patients' survival with this disease is short. According to the literature, approximately 60-70% of patients present relapse and death within three years after diagnosis[7]. One treatment option is intraperitoneal chemotherapy, which can be administered as hyperthermic intraperitoneal chemotherapy (HIPEC)[11]. HIPEC is indicated if the patient presents at least a partial response to neoadjuvant chemotherapy.

One limitation of radiotherapy in this tumor is the low tolerance of intraabdominal organs, ruling out curative doses. Radiotherapy is thus used as palliation[7]. DSRCT thus carries a poor prognosis, with survival of approximately 12 to 24 months after diagnosis, even with aggressive treatment regimens[7]. The association of cytoreductive surgery and HIPEC thus constitutes a treatment option for local control of an extensive abdominal tumor or treatment-resistant tumors with diverse histologies[12].

We report the case of a 7-year-old patient with DSRCT enrolled in the Pediatric Oncology Service of the National Cancer Institute José Alencar Gomes da Silva (INCA), treated with neoadjuvant chemotherapy followed by cytoreductive surgery and HIPEC for a desmoplastic small round cell tumor (DSRCT).

CASE REPORT

A 7-year-old male child presented with abdominal pain and increased abdominal volume, fever, and weight loss for 17 days. Thoracic, abdominal, and pelvic computed tomography was performed, revealing a large infiltrative abdominal tumor, ascites, and juxta-parietal lesion in the right hemithorax and diaphragm (Figure 1).

A Tru-Cut needle biopsy was performed, and histology showed DSRCT, with positive immunohistochemistry for AE1/AE3, EMA, desmin, CD99, CD56, EMA, focal CAM5.2, and focal CK5, and negative IHC for WT1, LCA, and myogenin. No molecular study of the tumor was performed.

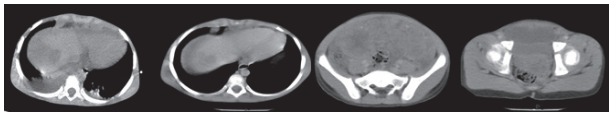

Figure 1. CT at admission: juxta-parietal tumor in right hemithorax, anteriorly, with another focus of lesion adjacent to right diaphragm; voluminous ascites; liver with hypodense lesion in segment IVa, adjacent to the hepatophrenic ligament, measuring 28 x 27 mm; abdominopelvic tumor

Initial tests showed metastases to the liver and lungs. Neoadjuvant chemotherapy was initiated according to the South American Study for Treatment of Patients with Metastatic Ewing Family of Tumors (GALOP), consisting of cycles of vincristine (1.5 mg/m^2/day, D1), doxorubicin (37.5 mg/m^2/day, D1 and D2), and cyclophosphamide (1,200 mg/m^2/day, D1) alternated with cycles of etoposide (165 mg/m^2/day, D1 to D3) and ifosfamide (3,000 mg/m^2/day, D1 to D3) every 15 days.

After 12 weeks of chemotherapy, imaging tests were showed that all the above-mentioned lesions were in regression, including disappearance of the ascites (Figure 2).

Figure 2. Liver with hypodense nodule measuring 1.8cm, located in segment VIII. Peritoneal nodule next to anterior upper edge of the right hepatic lobe, with dimensions maintained, containing focal calcification. Heterogeneous lobulated expansive formations occupying the hypogastric and pelvic regions, slightly smaller than those in the previous tests and more areas of cystic/necrotic degeneration

Patient was submitted to cytoreductive surgery, consisting of complete resection of the pelvic, mesocolon, peritoneal, and sigmoid tumors and all suspicious lesions. A lesion that had been described in the preoperative CT as a hepatic nodule was seen in surgery as a diaphragmatic lesion adhered to hepatic segment VII and was totally resected.

After complete surgical removal of all the visible and palpable tumors, the team proceeded to HIPEC, consisting of the introduction of temperature probes, four abdominal tube drains for inflow and outflow of the continuous perfusion liquid, which consisted of four liters of dextrose 1.5% and cisplatin 100 mg/m^2 heated to 40-41°C. This procedure lasted 60 minutes (Figure 3).

Liquid leaked in the thoracic region through a communication via the diaphragmatic suture, requiring

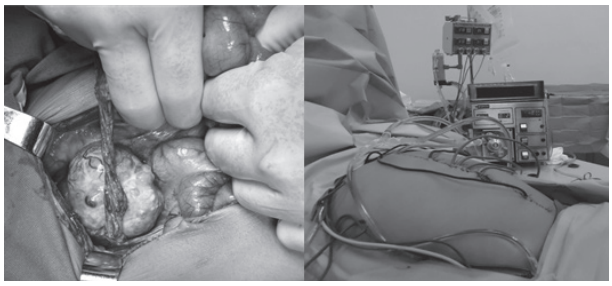

Figure 3. Tumor occupying pelvic cavity (left) and HIPEC procedure by closed technique (right)

right pleural drainage. Two abdominal drains in both flanks remained in the postoperative period. The entire procedure lasted approximately six hours and 30 minutes, under inhalational and peridural general anesthesia.

As a postoperative complication, the patient presented intense and difficult-to-manage abdominal pain. Analgesia was necessary with venous fentanyl at 2 mcg/kg/h and ropivacaine 0.1% via continuous infusion in peridural catheter, initially at 3 ml/h. Since the intense abdominal pain persisted, the peridural analgesia with ropivacaine was increased to 0.2% and fentanyl to 2.5 mcg/ml, totaling a volume of 4.5 ml/h. The patient still remained in intense pain. The decision was made to suspend venous fentanyl and initiate fentanyl via transdermal patch at 75 mcg/h and gabapentin 300 mg. On the third day post-op, dextroketamine 20 mcg/kg/min was added, replaced with **dexmedetomidine** 0.5 mcg/kg/h on the following day. On day four, the thoracic drain and one abdominal were removed. The other abdominal drain was removed on day six. The patient's pain improved significantly after these drains were removed. Patient remained in use of ropivacaine via peridural catheter until day nine post-op, when it was suspended.

As adjuvant treatment, the patient received four more cycles of chemotherapy and radiotherapy in the entire abdomen, including the diaphragm, the latter with a total dose of 18 Gy.

At the end of treatment, the patient was well and the imaging tests did not show any active disease. Six months into outpatient follow-up, the tumor relapsed in the mediastinum.

After discussion with the team and family, it was decided to perform palliative oral chemotherapy with cyclophosphamide (50 mg/m^2/day) and topotecan (0.8 mg/m^2/day) for 14 consecutive days every 21-28 days. The patient remained stable for 14 cycles of oral chemotherapy. At the end of this period, he presented a new progression of the thoracoabdominal lesions, culminating in death 14 months after the relapse. Overall survival was two years and seven months after diagnosis.

The current study was approved by the Institutional Review Board of INCA, protocol CAAE: 61797616.2.0000.5274. Authorization for publication was provided by the patient's parents by signing the free and informed consent form.

DISCUSSION

DSRCT is a rare aggressive sarcoma that presents with multiple peritoneal nodules[12]. Despite multimodal treatment, including chemotherapy, radiotherapy, and cytoreductive surgery, most patients experience recurrent or treatment-resistant disease[13-15]. Five-year survival rate is 15%[16,17], with mean survival of 17 months[4].

The high recurrence rate and difficulty in complete local resection justify innovation in management of the disease. The combination of cytoreductive surgery and HIPEC was first described by Spratt in peritoneal pseudomyxoma and implemented by Sugarbaker[18].

HIPEC is considered an additional strategy that allows microscopic elimination of the disease after cytoreductive surgery. This therapeutic approach can improve disease-free survival in selected patients[16,19]. Hayes-Jordan *et al.*, in a series of patients with DSRCT, showed that this procedure can be safe in children, consistent with our case report, but HIPEC was only performed in eight patients with DSRCT, and more patients are needed to prove therapeutic efficacy in this disease[12].

The method's key principles are treatment of the macroscopic malignant peritoneal disease with cytoreductive surgery and HIPEC immediately afterwards for treatment of the microscopic peritoneal disease. During the surgical act, it is essential to resect all the tumors greater than 1 mm, because the solution containing the chemotherapy is unable to penetrate lesions greater than 1-2 mm[19-21].

The best treatment results for DSRCT can be obtained with the combination of neoadjuvant chemotherapy, cytoreductive surgery, and adjuvant radiotherapy[13]. Complete surgical resection gives a survival advantage. Morphoproteomic profile studies in DSRCT demonstrated activation of the mTOR signaling pathway, indicating a potential for molecular targeted therapy [22]. However, the approaches described, such as HIPEC, intensity-modulated radiotherapy (IMRT), bone marrow transplantation, and targeted therapy have not proven effective to date[6,23].

CONCLUSION

Cytoreductive surgery associated with HIPEC can be performed and is well-tolerated, without increasing

morbidity. DSRCT is a rare disease with poor prognosis. This strategy allowed temporary control of the disease with good quality of life for the patient. It is not possible to claim that the procedure increased disease-free survival, since the patient's overall survival was two years and seven months. More studies are necessary to improve our knowledge of this disease and thus increase the odds of cure for patients.

CONTRIBUTIONS

Simone de Oliveira Coelho and Fernanda Ferreira da Silva Lima participated in the research project design, interpretation of the results, development of the manuscript, and analysis and revision of the final version for publication. Marilia Fornaciari Grabois and Fabiola Almeida Barros Rebêlo contributed to the research design, interpretation, and critical analysis of the intellectual content and approval of the version for publication.

Ricardo Vianna de Carvalho contributed to the surgical experiments, interpretation of the results, review of the patient's charts, study design, and elaboration of the final text. Sima Esther Ferman participated in the interpretation of the results and elaboration of the manuscript for publication. Odilon Souza Filho contributed to the revision and approval of the final version for publication.

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CONFLICT OF INTEREST

None.

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REFERENCES

1. Atallah V, Honore C, Orbach D, Helfre S, Ducassou A, Thomas L, et al. Role of adjuvant radiation therapy after surgery for abdominal desmoplastic small round cell tumors. Int J Radiation Oncol Biol Phys. 2016;95(4):1244-53.
2. Chang, F. Desmoplastic small round cell tumors: cytologic, histologic, and immunohistochemical features. Arch Pathol Lab Med. 2006;130(5):728-32.
3. Antonescu CR, Gerald W. Desmoplastic small round cell tumour. In: World Health Organization; International Agency for Research on Cancer. Pathology and genetics of tumours of soft tissue and bone. Lyon: IARC Press; 2002. p. 216-18.
4. Gerald WL, Miller HK, Battifora H, Miettinen M, Silva EG, et al. Intra-abdominal desmoplastic small round cell-tumor. Report of 19 cases of a distinctive type of high-grade polyphenotypic malignancy affecting young individuals. Am J Surg Pathol. 1991;15(6):499-513.
5. Bisogno G, Roganovich J, Sotti G, Ninfo V, di Montezemolo LC, Donfrancesco A, et al. Desmoplastic small round cell tumour in children and adolescents. Medical and Pediatric Oncology. 2000;34(5):338-42.
6. Mandal PK, Adhikari A, De A, Mondal SK. Desmoplastic small round cell tumor: Diagnostic dilemma and uncertain prognosis: report of few cases. J Can Res Ther. 2015;11(4):1028.
7. Hayes-Jordan A, Peter M, Anderson PM. The diagnosis and management of desmoplastic small round cell tumor: a review. Curr Opin Oncol. 2011;23(4):385-9.
8. Quaglia MP, Brennan MF. The clinical approach to desmoplastic small round cell tumor. Surg Oncol. 2000; 9(2):77-81.
9. Biswas G, Laskar S, Banavali SD, Gujral S, Kurkure PA, Muckaden M, et al. Desmoplastic small round cell tumor: extra abdominal and abdominal presentations and the results of treatment. Indian J Cancer. 2005;42(2):78-84.
10. Hassan I, Shyyan R, Donohue JH, Edmonson JH, Gunderson LL, Moir CR, et al. Intraabdominal desmoplastic small round cell tumors: a diagnostic and therapeutic challenge. Cancer. 2005;104(6):1264-70.
11. Honore C, Amroun K, Vilcot L, Mir O, Domont J, Terrier P, et al. Abdominal Desmoplastic Small Round Cell Tumor: Multimodal Treatment Combining Chemotherapy, Surgery, and Radiotherapy is the Best Option. Ann Surg Oncol. 2015;22(4):1073-79.
12. Hayes-Jordan A, Green H, Fitzgerald N, Xiao L, Anderson P. Novel treatment for desmoplastic small round cell tumor: hyperthermic intraperitoneal perfusion. JPS. 2010;45(5):1000-06.
13. Hayes-Jordan A, Green HL, Lin H, Owusu-Agyemang P, Fitzgerald N, et al. Complete Cytoreduction and HIPEC Improves Survival in Desmoplastic Small Round Cell Tumor. Ann Surg Oncol. 2014;21(1):220-24.
14. Ladanyi M, Gerald W. Fusion of the EWS and WT1 genes in the desmoplastic small round cell tumor. Cancer Res. 1994;54(11):2837-40.

15. Park BJ, Alexander HR, Libutti SK, Wu P, Royalty D, et al. Treatment of primary peritoneal mesothelioma by continuous hyperthermic peritoneal perfusion (CHPP). Ann Surg Oncol. 1999;6(6):582-90.
16. Msika S, Gruden E, Sarnacki S, Orbach D, Philippe-Chomette P, et al. Cytoreductive surgery associated to hyperthermic intraperitoneal chemoperfusion for desmoplastic round small cell tumor with peritoneal carcinomatosis in young patients. Journal of Pediatric Surgery. 2010;45(8):1617-21.
17. Lal DR, Su WT, Wolden SL, Loh KC, Modak S, et al. Results of multimodal treatment for desmoplastic small round cell tumors. J Pediatr Surg. 2005;40(1):251-5.
18. Elias D, Goéré D, Dumont F, Honoré C, Dartigues P, et al. Role of hyperthermic intraoperative peritoneal chemotherapy in the management of peritoneal metastases. European Journal of Cancer. 2014;50(2):332-40.
19. Gilly FN, Cotte E, Brigand C, Monneuse O, Beaujard AC, et al. Quantitative prognostic indices in peritoneal carcinomatosis. Eur J Surg Oncol. 2006;32(6):597-601.
20. Los G, Mutsaers PH, van der Vijgh WJ, Baldew GS, de Graaf PW, et al. Direct diffusion of cis-diamminedichloroplatinum(II) in intraperitoneal rat tumors after intraperitoneal chemotherapy: a comparison with systemic chemotherapy. Cancer Res. 1989;49(12):3380-4.
21. van de Vaart PJ, van der Vange N, Zoetmulder FA, van Goethem AR, van Tellingen O, et al. Intraperitoneal cisplatin with regional hyperthermia in advanced ovarian cancer: pharmacokinetics and cisplatin-DNA adduct formation in patients and ovarian cancer cell lines. Eur J Cancer. 1998; 34(1):148-54.
22. Subbiah V, Brown RE, Jiang Y, Buryanek J, Hayes-Jordan A, Kurzirock R, et al. Morphoproteomic profiling of the mammalian target of rapamycin (mTOR) signaling pathway in desmoplastic small round cell tumor (EWS/WT1), Ewing's Sarcoma (ES/FLI1) and Wilms' Tumor (WT1). Plos One. 2013;29;8(7):1-7.
23. Mir O, Adam J, Honoré C. Optimal multimodal treatment of desmoplastic small round cell tumors. JAMA Oncol. 2018;4(9):1301-1302.

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