Original Article

Desmoplastic small round cell tumor: Extra abdominal and abdominal presentations and the results of treatment

Biswas G, Laskar S*, Banavali SD, Gujral S, Kurkure PA, Muckaden M*, Parikh PM, Nair CN**

Department of Medical Oncology, *Department of Radiation Oncology, **Department of Pathology, Tata Memorial Center, Mumbai

Correspondence to: Dr. Chandrika N Nair, E-mail: cnnair98@hotmail.com

Abstract

BACKGROUND: Desmoplastic small round cell tumor (DSRCT) is a rare malignant neoplasm of adolescent males. Current multimodality treatment prolongs life and rarely achieves cure. **AIM**: To review the presenting features, histopathology and outcome of 18 patients with DSRCT treated at a single institution. **SETTING AND DESIGN**: This is a retrospective observational study of patients with DSRCT who presented at the Tata Memorial Hospital between January 1994 to January 2005. **MATERIALS AND METHODS:** Eighteen patients of DSRCT seen during this period were evaluated for their clinical presentation, response to chemotherapy and other multimodality treatment and overall survival. The cohort of 18 patients included 11 males (61%) and 7 females (39%) with a mean age of 16 years (Range 1½ - 30 years). Majority (83%) presented with abdomino-pelvic disease. The others, involving chest wall and extremities. There were 6 patients (33%) with metastatic disease at presentation. **RESULTS:** The treatment primarily included a multimodality approach using a combination of multiagent chemotherapy with adjuvant surgery and radiotherapy as applicable. A response rate of 39% (CR-1, PR-6), with chemotherapy was observed. The overall response rate after multimodality treatment was 39% (CR-5, PR-2). The overall survival was poor except in patients who had complete excision of the tumor. **CONCLUSION:** Abdomino-pelvic site was the commonest presentation, the disease can occur at other non-serosal surfaces also. Despite aggressive treatment the outcome was poor. However, complete surgical excision seems to provide a better survival.

Key words: Desmoplastic round cell tumor, Management and outcome

Introduction

Desmoplastic small round cell tumor is a rare malignant neoplasm. It is characterized by a distinct immunohistochemical profile and a recurrent, specific, chromosomal translocation. It is an aggressive and often misdiagnosed neoplasm of children and young adult. [1,2] This tumor has predilection for involvement of the peritoneum. CT features are frequently multiple bulky heterogeneous and necrotic soft tissue masses in the abdomen, usually without any obvious organ base. It is sometimes associated with ascites, adenopathies and liver metastases.

Typically, tumors consist of small, undifferentiated cells or spindle cells invested within an abundant desmoplastic stroma. Immunohistochemical studies show polyphenotypic differentiation with expression of epithelial, neural and muscle markers. [1]

A recurrent specific chromosomal abnormality t (11:22) (p13:q12) has been reported in DSRCT. [3] The breakpoints in this translocation involve two genes EWS, which is altered in the t (11:22) (q24:q12)

rearrangement characteristic of the Ewing's family of tumors and WT1, which is a Wilms tumor gene. EWS–WT1 chimeric transcripts are considered diagnostic of this disease. [4,5]

Current treatment protocols include multiagent chemotherapy and adjuvant surgery and radiotherapy. [6,7] Several chemotherapy regimens including alkylating agents and aggressive chemotherapy regimen followed by myeloblative therapy and stem cells rescue have been tried. [8] However, the emphasis is on achieving a complete and durable response. We report our experience in the management of DSRCT at our center.

Materials and Methods

18 patients diagnosed as DSRCT at our institute for management during the period 1994 to 2005 are included this analysis. The diagnosis was based on routine histopathology and the radiological findings. Histopathological evaluation of tumor was done using H & E Microscopy and Immunohistochemistry (IHC). IHC was done for eleven cases. Complete physical and radiological evaluation and metastatic workup using CT scan Thorax/Abdomen/Pelvis, Bone scan, Bone marrow aspiration and biopsy was done for most patients. 6 patients had metastatic disease at presentation. The chemotherapy schedules received by the patients are documented in Table: I. At the end of 8-9 weeks of induction chemotherapy, patients were evaluated for local treatment when feasible. Surgery alone or in combination with radiotherapy was used for local treatment. This was followed by maintenance chemotherapy. The outcome and survival of these patients are documented in Table: II (C).

Results

The clinical, radiological, treatment received and the outcome and survival of these patients are shown in the Table: II (A, B, C).

The age ranged from 1½ year to 30 years. Ten patients were in the pediatric age group (≤ 15 years) and seven were females. Fifteen patients presented with abdomino-pelvic swellings, of which 3 had ovarian mass. One patient had chest wall swelling (Case no. 7) and another patient had an ulcerative mass in the palm of the right hand (Case no. 9). There was no bone marrow involvement among 15 patients done. Bone scan was abnormal in one patient among the 11 patients done. LDH was raised in 6 out of 8 cases done, which probably signify disease load. In cases 13 and 15 we did pre-treatment CA.125, which were significantly raised. We could perform diagnostic EWS-WT1 in case no.17 was positive. The response seen with chemotherapy was 39% (CR-1, PR-6). One had Stable disease and rest was considered to have Progressive disease including those not evaluable for response. In total there were 8 surgeries (Outside-4, TMH-4). There were only 3 complete excision including negative cut margins. 4 patients received radiotherapy including one that received Stereotactic technique. The details of the three unusual primary site of involvement (Case no: 7, 9 & 18) are as follows:

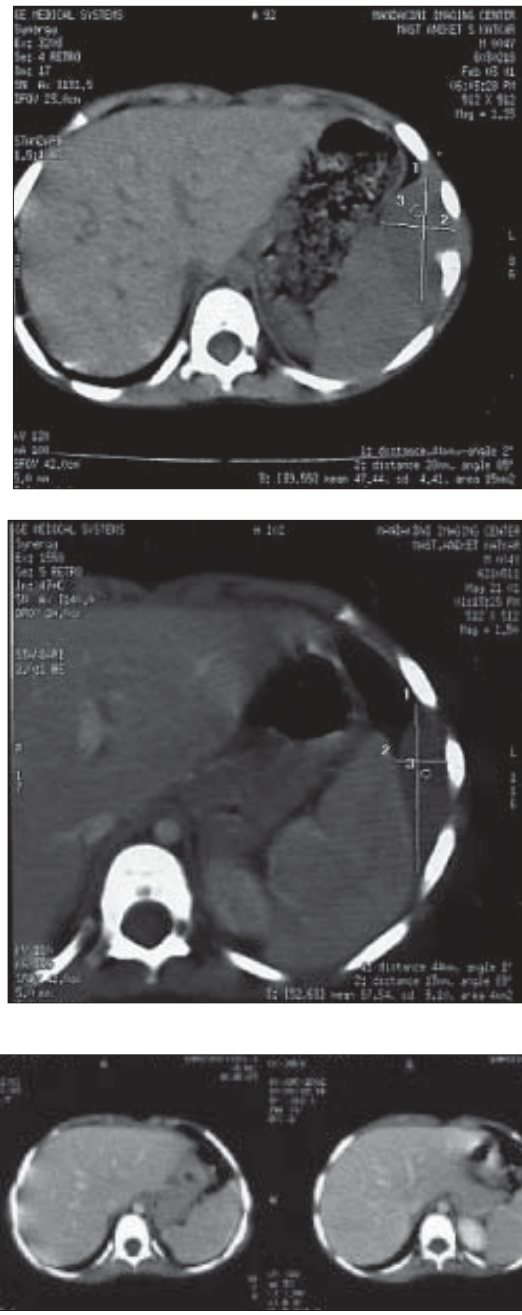


Figure 1: CT scan of the chest (Case No. 7) a) Showing the chest wall tumor at presentation, b) Showing partial response to chemotherapy, c) Showing no evidence of disease at 24 months

Case no. 7

CT scan revealed a soft tissue mass in the left lower lateral chest wall encasing the lateral portion of the left 9th rib which showed sclerosis and speculated periosteal reaction. The intra thoracic component of the mass was larger than the extra thoracic component. There was no evidence of calcification or ossification (Fig: 1, a). On histopathology (Fig: 3, a & b) the tumor cells were positive for CK, EMA, Vimentin, Desmin, NSE, Myoglobin and was negative for S100 and LCA. A diagnosis of DSRCT was made in view of the polyphenotypic expression by the tumor cells. With induction of EFT 2001 protocol (Table: I), the tumor showed partial response (Fig: 1, b). Complete excision of the tumor was then done. The histopathology of the specimen showed residual tumor and showed divergent differentiation predominantly peripheral neuroectodermal and also epitheloid differentiation with CK being positive. The cut margins were positive for tumor. He then received radiotherapy (5040cGy) followed by maintenance therapy of EFT 2001 protocol. CT scan at 24 months is depicted in Fig. 1, c. At 57 months (April 2005) he is alive and disease free.

Case no. 9

A 2½-year-old female child presented with a large ulcerative mass in the palm of the right hand. The biopsy revealed high grade malignant tumor with tumor cells showing varied morphology from round to oval to epitheloid features and no desmoplasia was seen. The tumor cells were positive for Cytokeratin, Vimentin, NSE and Chromogranin and were negative for Desmin, MyoD, Myoglobin, CD 30, HMB 45, CD20, and MIC 2. This patient had poor response to chemotherapy schedule ie. VAC regimen (Table: I). She underwent above wrist amputation. The histopathology of tumor showed epithelial and mesenchymal markers. She was continued on maintenance chemotherapy. However after 4½ months she developed right axillary mass. This mass was excised along with the nodes. The histopathology of the mass showed high-grade malignant round cell tumor showing polyphenotypic expression and the tumor showed extensive desmoplasia. The nodes were negative for any malignant cells. The child did not receive further treatment.

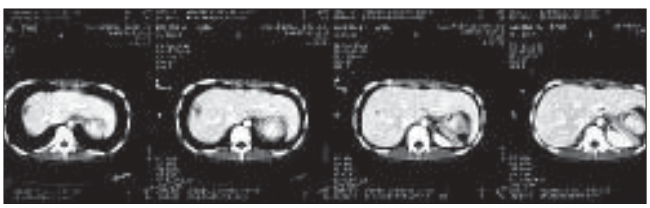
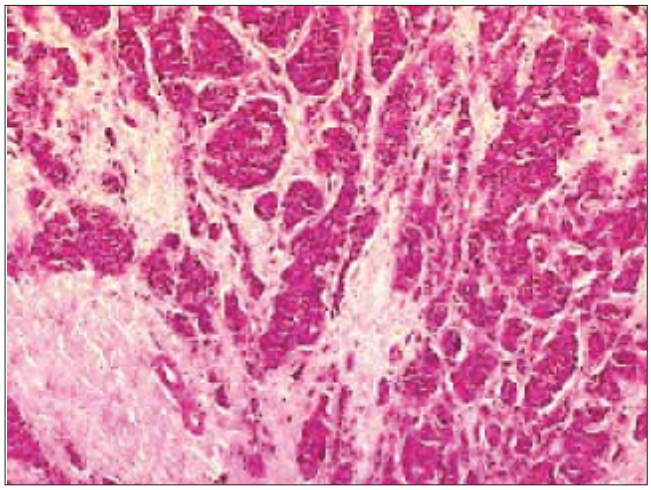
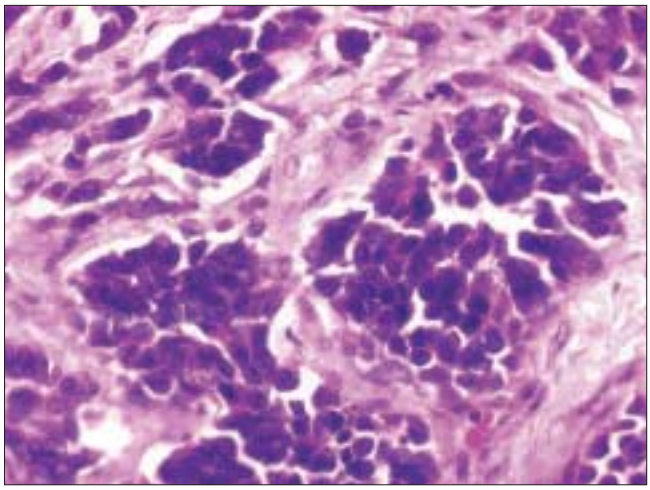


Figure 2: CT scan of the abdomen (Case No. 10) a) Showing liver metastasis



3 (a)



3(b)

Figure 3: Histopathological slides (Case No. 7) a) Tumor islands with intervening desmoplastic stroma, b) Islands composed of malignant round cells

Case no. 18

This one and half year old female child presented with a large well defined soft tissue mass seen predominantly along postero-lateral aspect of left thigh with lamellated type of periosteal reaction seen involving the entire shaft of femur. The histopathology was suggestive of DSRCT. She received 3 cycles of induction treatment of RCT-II and subsequently lost to follow up.

Response was seen in 7 (n = 18) patients. CR achieved in one and PR in six patients. One had stable disease. Seven had documented progressive disease and

Table I: Chemotherapy schedules

A.	Round Cell Tumour (RCT) - II protocol								
Induction									
Week	0		3		5		8		
	V		V		V		V		
	I		A		I		A		
	E		C		E		C		
Cycle	1		2		3		4		
Maintenance: Alternate cycle of VAC & VCD (total 12 cycles)									
B.	Ewing's Family of Tumor EFT - 2001 protocol								
Week	0	1	2	3	4	5	6	7	8
	V	V	V	V	V	V	V	V	V
	I			I			A		A
	E			E			C		C
Cycle	1			2			3		4
Maintenance: 2 cycles of VIE followed by alternate cycles of VAC and VCD (total 8 cycles)									
C.	IVA protocol								
	I			1.2gm/m^2 daily (d1-3) with Mesna					
	V			1.4mg/m^2 daily (d1, 8, 15)					
	A			40mg/m^2 (d1)					
Repeat cycle every month									
D.	Weekly VAC protocol								
	V			1.4mg/m^2 wkly for 8 wks					
	A			60mg/m^2 wk 1 and 5					
	C			500mg/m^2 wkly for 8 wks					
NB:	V = Vincristine			1.4mg/m^2					
	A = Adriamycin			60mg/m^2					
	C = Cyclophosphamide			600mg/m^2					
	I = Ifosfamide			2gm/m^2 daily (d 1 to d 5), with Mesna					
	E = Eotposide			100mg/M^2 daily (d 1 to d 5)					
	D = Dactinomycin			1mg/m^2					

3 patients were not evaluable for response and have been considered to have progressive disease.

Complete excision of the mass was also possible in case no 3. It was found to be an ovarian mass and there was no residual viable tumor. She was continued on 2 more cycles of chemotherapy. At 48 months, she was found to be disease free. Case no. 10 underwent upfront surgery. She had excision of the ovarian mass, excision of mesentery along with the nodules. The liver metastasis also showed response to chemotherapy. The liver metastasis (Fig. 2, a) was treated with using Extracranial Stereotactic Radiotherapy technique delivering a dose of 28Gy in 4 # @ 7Gy per # x 2 #/week. At 41 months (March 2005) she is alive and disease free. Case no. 14 presented with ascitis, peritoneal deposits, liver and splenic involvement. Post EFT-2001 protocol induction, he attained PR. Subsequently, completed EFT-2001 protocol maintenance. Post planned treatment PET scan showed diffuse uptake in liver and one focus in spleen. He was then started on oral chemotherapy with Etoposide, Thioguanine and Tamoxifen.

Overall survival has been poor except in the 3 cases where complete excision was possible. Other cases had disease progression locally. The median overall survival is 6.5 months (Range 1-57 m).

DISCUSSION

We are reporting unusual sites - chest wall, hand, thigh and ovary besides the common sites and the clinical outcome. Similar to all the series reported so far, the abdomino-pelvic site was the commonest site of presentation. Of these 3 cases primarily seems to be arising from the ovary. Other sites Pleura, Para-testicular, Lung, Ovary, thorax, intracranial, soft tissue, bone of the hand and Sino-nasal regions have been

Table II A: Patient Characteristics

No.	Initial	Age/Sex	Presentation	Primary	Mets	Stage
1	AS	10/F	Mass & pain abdomen	Abdomen	None	L
2	JP	11/F	Mass abdomen	Abdomen	None	L
3	YS	13/F	Mass abdomen	Abdomen	None	L
4	SI	30/M	Mass abdomen & pelvis	Abdomen & Pelvis	Regional nodes	L
5	NI	15/M	Mass abdomen	Abdomen	None	L
6	CN	19/M	Mass abdomen	Abdomen	Regional nodes	L
7	AK	4/M	Swelling chest wall	Thorax	None	L
8	SK	30/M	Mass abdomen & pelvis	Abdomen & Pelvis	None	L
9	SM	$2^{1/2}$ F	Swelling palm	Upper extremity	None	L
10	HK	16/F	Mass pelvis	Pelvis	None	L
11	SP	19/M	Mass abdomen & pelvis	Abdomen & Pelvis	Liver, Lung & SCLN	M
12	MA	23/M	Mass & pain abdomen	Abdomen	Inguinal nodes	M
13	SA	21/M	Mass & pain abdomen	Abdomen	Liver, Rib	M
14	SG	27/M	Swelling & pain abdomen	Abdomen	Liver	M
15	BT	13/F	Swelling & pain abdomen	Abdomen & Pelvis	Pleura	M
16	MS	14/M	Mass abdomen	Abdomen	Mediastinal & SC LN	M
17	SK	15/M	Mass abdomen	Abdomen	None	L
18	MC	$1^{1/2}$ F	Mass thigh	Lower extremity	None	L

L localized **M** metastatic **SCLN** supraclavicular lymph node

reported. [9-14, 20] DSRCT is commonly reported in children and young adults and male predominance is noted. [6] In our series also male predominance was seen. A high serum CA 125 level may be a specific marker for DSRCT, and thus may permit early diagnosis and treatment of this fast-growing tumor. [21,22] We have done in 2 patients at baseline and it was found to be significantly raised.

Most patients presented with extensive local disease. Distant metastases were seen in six patients. The most common site of distant metastases was Liver[18] (n=3/6). None had bone marrow involvement.
The diagnosis of DSRCT may be suspected in young men with multiple bulky heterogeneous peritoneal soft tissue mass. Imaging is useful for staging and also for guided biopsies. [18]

Markers for multilineage differentiation has been reported by Lae ME et al. [15] This group has found these tumors to be positive for Desmin (Dot pattern) in 81%, WT1 in 91%, Keratin in 87%, and Neuron Specific Enolase in 84% of the cases. The EWS-WT1 gene fusion transcript was detected in 29 of 30 times. Our patient (Case no. 9) showed polyphenotypic differentiation markers but did not show desmoplasia. However, the metastatic axillary mass later showed extensive desmoplasia along with polyphenotypic expression.

They require aggressive multimodality therapy.[18] Intensive chemotherapy and complete excision of the tumor would be required to achieve long term disease free survival. Often surgery is not feasible especially in the abdomino- pelvic tumors due to the extensive involvement. Whole abdomino-pelvic irradiation

Table II B: Treatment Details

No.	Outside t/t	CT Protocol	Sx	RT	Other T/t
1	Sx	RCT-II	Yes	No	Palliative care
2	-	RCT-II	No	No	-
3	-	Alternate (IVA)	Yes	No	-
4	-	RCT-II	No	No	Palliative care
5	-	RCT-II	No	No	Palliative care
6	-	RCT-II	No	No	Palliative care
7	-	EFT-2001	Yes	Yes	-
8	Sx	EFT-2001	Yes	No	-
9	-	Alternate (Wkly VAC)	Yes	No	Palliative care
10	Sx	EFT-2001	Yes	Yes	-
11	-	None	No	No	Palliative care
12	-	EFT-2001	No	No	Palliative care
13	-	RCT-II	No	Yes	Palliative care
14	-	EFT-2001	No	No	Oral chemo
15	Sx	Alternate (Wkly VAC)	Yes	No	Palliative care
16	CT	Alternate (ICE)	No	No	-
17	-	EFT-2001	Yes	Yes	-
18	-	RCT-II	No	No	-

CT Chemotherapy **RT** Radiotherapy **SX** Surgery

Table II C: Results & Survival

No.	Response to CT	Overall response	Progression	Status at LFU	Salvage t/t	Survival (FUD)
1	PD	PD	Yes	Dead with dx	None	7m
2	CR	CR	No	LFU	-	6m
3	PR	CR	No	Alive without dx	-	48m (August 2002)
4	PD	PD	Yes	Dead with dx	Yes (CT)	7m
5	PR	PD	Yes	Dead with dx	Yes (CT)	12m
6	PD	PD	Yes	Dead with dx	None	5m
7	PR	CR	No	Alive without dx	-	57m (April 2005)
8	NE	NE	-	LFU	-	1m
9	PD	PD	Yes	Dead with dx	Yes (Sx)	6m
10	PR	CR	No	Alive without dx	-	41m (March 2005)
11	NE	NE	-	Dead with dx	-	1m
12	SD	PD	Yes	Dead with dx	None	21/2m
13	PR	CR	Yes	Dead with dx	None	12m
14	PR	PR	No	Alive with dx	-	14m
15	PD	PD	Yes	Alive with dx	None	6m
16	PD	PD	Yes	Dead with dx	Yes (CT)	6m
17	PD	PR	Yes	Dead with dx	None	17m
18	NE	NE	-	LFU	-	3m

CR Complete response **PR** Partial response **SD** Stable disease **PD** Progressive disease
NE Not evaluable **LFU** Lost to follow up **FUD** Follow up duration

(WAPI) has been reported by Goodman KA et al, [16] as a novel approach for the residual disease following aggressive chemotherapy and debulking surgery. However, the overall survival and relapse free survival rate reported by them at 3 years were 48% and 19% respectively. Aggressive multimodality treatment followed by high dose Busulphan with autologous rescue resulting in a disease free survival of only 19 months post transplant is also reported. [8] Successful clinical response was reported by Philip M Rosoft et al with Irinotecan and hence suggests trials with Irinotecan alone or in combination. [17]

Current treatment prolongs life and rarely achieves cure. Neoadjuvant chemotherapy, greater than 90% tumor debulking, and radiotherapy have been shown to prolong survival. Future efforts must focus on cell-specific treatment protocols. [19]

The demerits of this analysis are absence of specific cytogenetics, non-uniformity of protocol and few aggressive surgeries.

Conclusion

Though abdomino-pelvic site is the commonest site of DSRCT, this malignancy can occur at other sites which are not associated with serosal surface and thus the histogenesis of this tumor still remains obscure.

Our experience shows that some degree of chemo-sensitivity is observed in DSRCT. However a complete surgical excision seems to improve survival. Results of treatment using current combined modality treatment remain unsatisfactory. There is a definite need to further risk stratify thus develop techniques and regimens for improving outcome.

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