A rare cause of bilateral pleural effusion – desmoplastic small round cell tumor

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Abstract

Desmoplastic small round cell tumor (DSRCT) is a rare, extremely aggressive and malignant tumor predominantly affects young adolescent males and typically presents as a large intra-abdominal mass. However, tumor arising from other body sites are also reported in the literature. Histology and immunohistochemistry play an important role in the diagnosis and differentiating this rare tumor from other round cell tumors. A multidisciplinary approach consisting of a combination of surgery, chemotherapy and radiation therapy is the treatment of choice as there is no standard therapy. We report a case of DSRCT of testis with pleural metastasis presenting as bilateral pleural effusion in a young adolescent male who was treated with both surgery and chemotherapy. However, the patient succumbed to illness after one year of diagnosis.

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Key words: Desmoplastic small round cell tumor; DSRCT; pleura; immunohistochemistry.

Ethics approval and consent to participate: No ethical committee approval was required for this case report by the Department, because this article does not contain any studies with human participants or animals.

Conflict of interest: The authors declare that they have no competing interests, and all authors confirm accuracy.

Contributions: AB, PM, designed case report; AB, AC, data collection; PM, HN, data analysis; AB, PM, AC, manuscript drafting. All the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Acknowledgements: The Authors would like to thank Dr. Savithri Ravindra (Pathologist) for providing the HPE slides.

Received for publication: 1 April 2021.
Accepted for publication: 6 October 2021.

Monaldi Archives for Chest Disease 2022; 92:1874
doi: 10.4081/monaldi.2021.1874

Introduction

Desmoplastic small round cell tumor (DSRCT) is a rare and highly aggressive neoplasm with characteristic histological, immunohistochemical pattern and chromosomal translocation features, first described as a distinct clinico-pathologic entity by Gerald and Rosai in 1989 [1]. These tumors predominantly occurs in young adolescent males and primarily occurs in the abdomen and pelvis [1,2]; however, tumor arising from other locations are also reported. The tumor possesses a diagnostic challenge due to its rarity and also due to the absence of specific clinical manifestations and similar morphologic appearances which it shares with other small round cell tumors. Prognosis is poor owing to advanced stage at presentation and lack of standard therapy. Only few cases of pleural involvement by DSRCT (<15 cases) have been reported in the scientific literature. We report a case of DSRCT of testis with pleural metastasis presenting as bilateral pleural effusion.

Case Report

A 25-year-old male presented with dyspnea on exertion, left sided chest pain, fever with chills and dry cough for three weeks. He had lost three kgs of weight in one month and was an occasional smoker. On examination, he had tachypnea, tachycardia and room air saturation was 92%. Head to toe examination was normal except for a right testicular swelling which the patient had not noticed. Respiratory system examination revealed absent breath sounds over bilateral infrascapular regions. Other systemic examination was normal. Routine blood investigations including complete blood picture, liver and renal function tests were normal. Arterial blood gas (ABG) showed type 1 respiratory failure. Chest X-ray of the patient on day 1 showed bilateral pleural effusion (Figure 1a) and ultrasound abdomen showed enlarged retroperitoneal lymph nodes. Therapeutic pleural fluid aspiration was done on right side and 300 ml of straw-colored fluid was aspirated and analysis revealed exudative fluid with high adenosine deaminase (ADA) levels and negative malignant cytology. Thorax CT (Figure 1b) and abdomen done on day 4 showed right mild and left gross pleural effusion, borderline hepatosplenomegaly, heterogeneously enhancing nodal mass in retroperitoneal region encasing and anteriorly displacing aorta (Figure 1c), inferior vena cava and

branches of aorta and a right testicular mass lesion (Figure 1d). As there was high degree of suspicion for malignancy, β HCG and Alpha fetoprotein were done which were within normal limits. Patient underwent right high orchidectomy. Even as the above reports were expected, patient became more breathless and had recurrent pleural effusion for which needle biopsy of pleura using Abram's needle was done followed by pigtail insertion, later pleurodesis using 100 ml of 2% iodopovidone on left side. Histopathology of testicular mass revealed features of small round cell tumor (Figure 2a). Left pleural biopsy also revealed metastatic small round cell tumor (Figure 2b). Immunohistochemistry of pleura (Figure 3) was strongly positive for desmin and focal positivity for neuron specific enolase (NSE) and Wilms tumor (WT1). FISH (fluorescence *in situ* hybridization) analysis was negative for EWSR1 (22q12) gene translocation. A diagnosis of DSRCT of testis with pleural metastasis was made.

Patient was started on alternate regimen of IV vincristine, adriamycin, cyclophosphamide and ifosfamide, etoposide every three weeks. Plan was to complete 17 cycles. PET scan showed near complete response at the end of sixth cycle. However, at the end of 14 cycles, he developed ascites and obstructive jaundice. Repeat PET scan showed features of progressive disease and he succumbed to death one year after diagnosis.

Discussion

Desmoplastic small round cell tumor is an extremely rare and highly aggressive malignancy, with an estimated incidence is 0.2-0.5 per million people. These tumors predominantly occurs in young males in their second or third decade of life, male > female (5:1) predilection. It typically presents as a large intra-abdominal mass originating from the abdominal cavity and pelvis; thus, the retro peritoneum, omentum, and mesentery are often involved. Although extra abdominal DSRCT is rare, invasion of extra peritoneal sites like testis, ovaries, lung, pleura, intracranial, soft tissue and bone, parotid gland are also reported [3,4]. DSRCT needs to be differentiated from other round cell tumors (Table 1).

Invasion of pleura by DSRCT is extremely rare and challenging to diagnose, because of their rarity and unspecific demographic, clinical, and radiological features. It commonly presents with chest pain, dyspnea, cough and back pain. Different radiological manifestations of pleural invasion by DSRCT include diffuse irregular or nodular pleural thickening, unilateral or bilateral pleural effusion [4], multiple pulmonary nodules or solid mass in thorax.

Among the extra abdominal metastases of DSRCT, Bellah *et al.* [5] and Biswas *et al.* [6] reported pleural effusion in only two out of 11 patients and one out of 18 patients respectively. In majority of previously reported cases of pleura invasion by DSRCT, left pleura

Table 1. Differential diagnosis of small round cell tumor.

Ewing's sarcoma/peripheral neuroectodermal tumor
Neuroblastoma
Rhabdomyosarcoma
Wilm's tumor
Non-Hodgkin's lymphoma
Synovial sarcoma
Desmoplastic small round cell tumor
Small cell carcinoma
Retinoblastoma
Hepatoblastoma
Nephroblastoma
Small cell osteogenic sarcoma
Granulocytic sarcoma

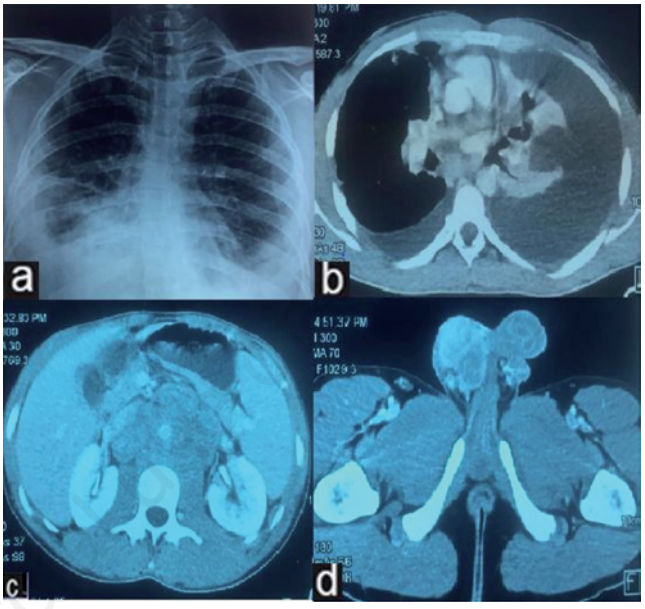

Figure 1. a) Chest X ray showing bilateral pleural effusion; b) axial cut section CT thorax showing bilateral pleural effusion L>R; c) CT abdomen showing heterogeneously enhancing nodal mass in retroperitoneal region encasing and anteriorly displacing aorta; d) CT pelvis showing large right testicular mass lesion.

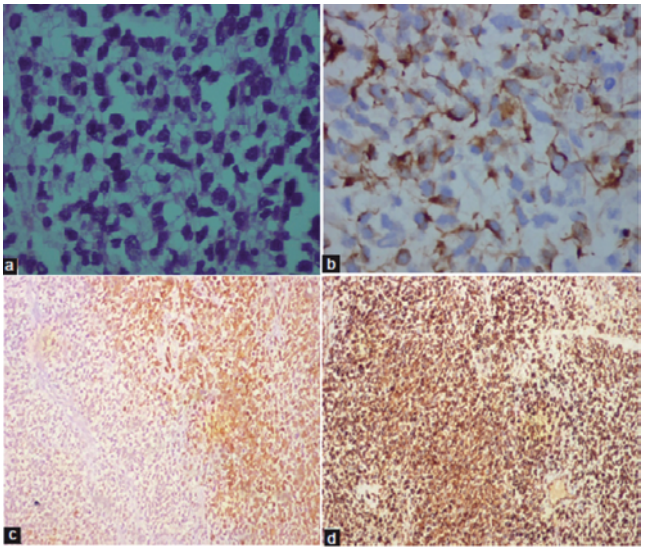

Figure 2. a) Pleural biopsy showing small round blue cells separated by abundant desmoplastic stroma (H&E staining x100); b) immunohistochemical positivity for desmin in pleural biopsy; c) positivity for neuron-specific enolase (NSE); d) positivity for WT1.

was involved in 46.7%, right pleura in 26.7% and bilateral in 20% of the cases in the form of pleural effusion [7]. Similarly in a study involving 60 patients of abdominal DSRCT, pleural effusion was the presentation only in 5% of patients and also pleural effusion was identified as a potential risk factor for adverse outcome [8].

It has been suggested that this tumor may be derived from the primitive mesothelium or submesothelial mesenchyme. Characteristic histologic features of DSRCT include well-defined nests composed of small round cells, separated by abundant desmoplastic stroma. A definite diagnosis can be made with a demonstrated multidirectional differentiation from other round cell tumors and coexpression of epithelial [cytokeratin (CK) and epithelial membrane antigen (EMA)], mesenchymal (vimentin and desmin) and neural (CD56 and NSE) markers [9]. A distinct staining pattern for desmin, namely the punctuate and perinuclear cytoplasmic positivity is seen. Almost all DSRCTs are positive for WT1 genes. Cytogenetic study shows unique (11:22), (p13:q12) translocation which results in an active fusion protein involving the Ewing sarcoma (EWS) and WT1 genes, which was present in 29 out of 32 tumors in a study by Lae *et al.* [9]. EWSR1/WT1 fusion gene has shown to induce the upregulation of platelet-derived growth factor (PDGF) ligand and receptors, which might be responsible for the excessive production of desmoplasia in DSRCT.

There is no standard therapy for DSRCT. A multidisciplinary approach consisting of a combination of surgery, chemotherapy and radiation therapy is adopted in most cases in literature. Whole abdomino-pelvic irradiation (WAPI) as a novel approach for the residual disease following aggressive chemotherapy and debulking surgery has been reported with overall survival and relapse free survival rate of 48% and 19% respectively at the end of three years [10]. The most recent chemotherapy regimen employed is the "P6 protocol", which consists of cyclophosphamide, doxorubicin, vincristine, etoposide and ifosfamide [11].

Several other novel agents such as tyrosine kinase inhibitors - pazopanib, sunitinib, anti-VEGF agent - bevacizumab, insulin growth factor-1 receptor (IGF-1R) antibody - ganitumab, cixutumumab, mammalian target of rapamycin (mTOR) inhibitor - temsirolimus have all been reported to be well tolerated and having good antitumor activity in patients with pre-treated DSRCT. With the available best treatment modality, the overall survival rate is less than 44% at three years and only 15% at five years [12].

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