

Case Report

Management of locally advanced primary mediastinal synovial sarcoma

Ambarish S Chatterjee, Rajiv Kumar¹, Nilendu Purandare², Sabita Jiwnani, George Karimundackal, CS Pramesh

Departments of Surgical Oncology, ¹Pathology and ²Nuclear Medicine and Molecular Imaging, Division of Thoracic Oncology, Tata Memorial Centre, Mumbai, Maharashtra, India

ABSTRACT

Primary mediastinal synovial sarcoma (PMSS) is a relatively rare disease, and patients are treated predominantly with surgery for resectable disease. Management of locally advanced borderline resectable and unresectable PMSS is not only challenging but also lacks standard guidelines. We present three patients with PMSS, who were unresectable or borderline resectable at presentation and were treated with neoadjuvant chemotherapy followed by surgery and postoperative radiotherapy.

KEY WORDS: Locally advanced, neoadjuvant chemotherapy, primary mediastinal synovial sarcoma, R0-resection

Address for correspondence: Prof. C S Pramesh, Department of Surgical Oncology, Tata Memorial Centre, Parel, Mumbai - 400 012, Maharashtra, India.
E-mail: prameshes@tmc.gov.in

INTRODUCTION

Synovial sarcoma (SS) is a distinct soft tissue sarcoma with variable mesenchymal and epithelial differentiation and characterized by specific chromosomal translocation: T (X; 18) (p11.2; q11.2) which leads to formation of SS18(SYT)-SSX fusion gene. Primary mediastinal sarcoma is extremely rare and represents 1.4% of all sarcomas and SS accounts for 2% of all primary mediastinal sarcomas.^[1] Treatment modalities for primary mediastinal SS (PMSS) described in literature are surgery, chemotherapy and radiation in different combinations, surgery being the main-stay. A significant proportion of patients have locally advanced, unresectable, or borderline resectable disease^[2] and their management is a therapeutic challenge because of operative complexity, higher rates of incomplete resections, and lack of standard guidelines. SSs respond to chemotherapy and can be downstaged with chemotherapy to achieve R0-resection.

CASE REPORT

Three patients (all female, aged 16, 29, and 42 years) presented with facial puffiness and dysphagia, chest pain and exertional dyspnea with duration of symptoms ranging from 1 to 6 months. Two patients had Eastern Cooperative Oncology Group performance status (PS) of one while one had PS three. On imaging with contrast enhanced computed tomography scan, all patients had an anterior mediastinal mass with necrosis. The tumors ranged from 11.3 cm to 17.6 cm in maximum dimension [Figure 1] and abutted the great vessels in all patients; in one patient, the right main bronchus was also encased. There was associated consolidation of the adjacent lung parenchyma in all patients. A core biopsy from the solid component of the tumor showed SS in all three patients including two biphasic and one monophasic variant [Figure 2]. Diagnosis

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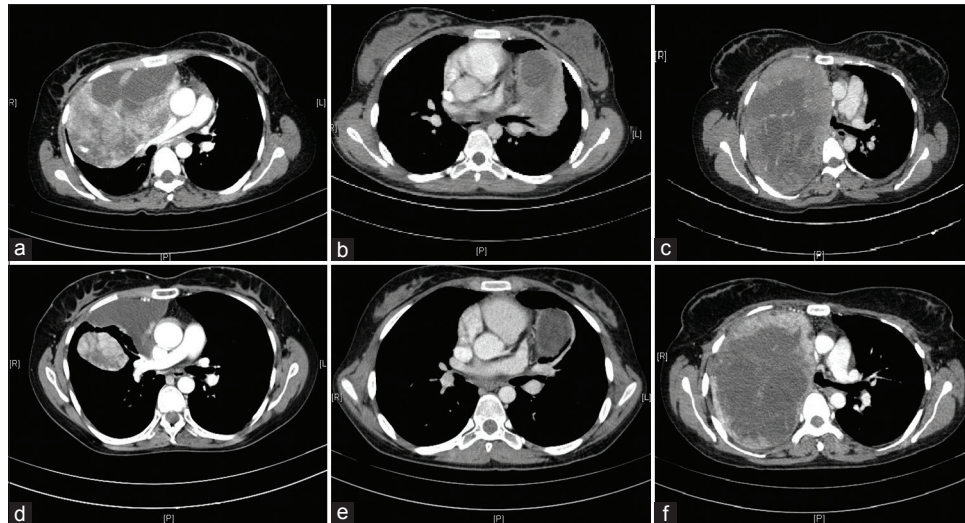


Figure 1: Contrast enhanced computed tomography scan showing response to neoadjuvant chemotherapy, (a-c) contrast enhanced computed tomography images at presentation, (d-f) contrast enhanced computed tomography images after neoadjuvant chemotherapy

was confirmed by immunohistochemistry in all three cases. The tumor cells were focally positive for epithelial markers, i.e., epithelial membrane antigen (EMA) and AE1/AE3 and diffusely positive for Mic-2 and Bcl2 and are negative for smooth muscle actin, H-caldesmon, CD34, and S100P. Translocation studies were not done as there was no ambiguity in diagnosis.

The thoracic oncology multidisciplinary team (MDT) decision was to initiate treatment with neoadjuvant ifosfamide and anthracycline-based chemotherapy because of borderline resectability or unresectability, suboptimal pulmonary function tests, and PS. Two patients received six cycles of ifosfamide and adriamycin while one patient received three cycles of Ifosfamide and Epirubicin. There was a considerable symptomatic improvement in all patients with the patient with PS3 converting to PS1 after six cycles of chemotherapy. Postchemotherapy, two patients had partial response, and one patient had stable disease with no serious toxicities [Figure 1 and Table 1]. After elaborate discussion within the MDT and with the patients, we decided to operate all three patients with a high risk, possible requirement of pneumonectomy or lobectomy, possible injury to adjacent structures, R+ resection, and intraoperative tumor spillage being explained.

A median sternotomy and mediastinal tumor excision were done in all three patients. In addition, patients required lung resections ranging from wedge resection (one patient), lobectomy (one patient) to pneumonectomy (one patient) [Figure 3]. Vascular resections included the excision of the brachiocephalic vein, ligation of the internal jugular vein, sacrificing the azygos vein, and phrenic nerve. Pleurectomy was required in one patient and excision of pericardium in another patient. The mean blood loss was 1200 ml. All patients had an uneventful postoperative recovery and were discharged with a mean hospital stay of 7 days.

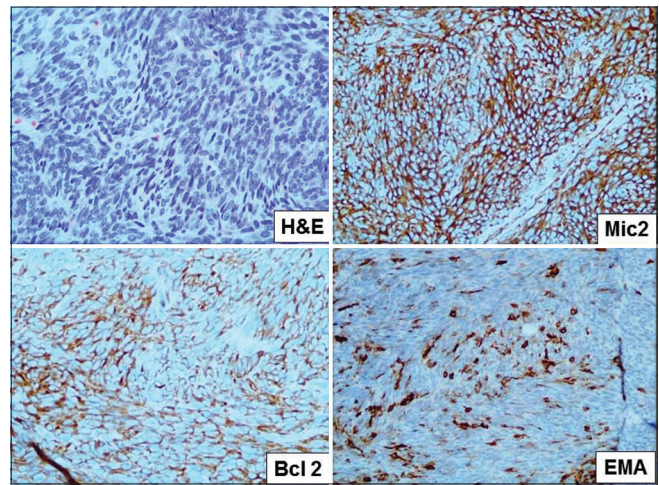


Figure 2: Histopathological examination revealed monophasic synovial sarcoma (H and E, $\times 400$) expressing Mic2, Bcl2 diffusely along with focal epithelial membrane antigen positivity (DAB, $\times 200$)

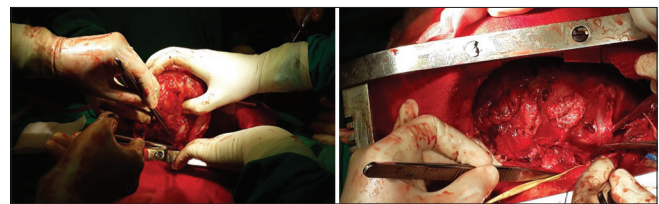


Figure 3: Intraoperative photographs showing the anterior mediastinal tumor

Histopathologically, all three patients had residual viable SS along with postchemotherapy related changes in the form of necrosis, hyalinization, and calcification. One patient had lung infiltration with vascular tumor thrombus. In all three cases, the soft tissue cut margins were close (0.1–0.2 cm away), however, technically free of tumor (R0-resection). After an MDT review, all three patients received adjuvant radiotherapy. The patients are

Table 1: Summary description of individual patients

PS (ECOG)	Radiology	Diagnosis	NACT	Response/toxicity	Surgery	PORT
ECOG 1	Anterior mediastinal mass with necrosis Abutting great vessels and compressing SVC Collapse consolidation of the left upper lobe	Synovial sarcoma Mic-2, EMA, and Bcl2 positive Negative for SMA, H-caldesmon, and S-100	Ifosfamide 1.8 g/m ² /day: Day 1-5 Mesna 600 mg: 0, 4, 8 h after ifosfamide - day 1-5 Adriamycin 60 mg/m ² Cycle every 3 weekly 6 cycles	Partial response No Grade 3/4 toxicity	Mediastinal tumor excision with left upper lobe wedge	59.4 Gy/33 [#] 1.8 Gy per fraction
ECOG 1	Mass in anterior mediastinum and right hemithorax Encasing the right main bronchus and the right pulmonary artery Part of the right lower lobe consolidation	Biphasic synovial sarcoma Mic-2, Bcl2 positive, epithelial cells positive for AE1/E3 CD34 negative	Ifosfamide 1.8 g/m ² /day: Day 1-5 Mesna 600 mg: 0, 4, 8 h after ifosfamide - day 1-5 Epirubicin 60 mg/m ² : Day 1, 8 Cycle every 3 weekly 3 cycles	Stable disease No grade 3/4 toxicity	Mediastinal tumor excision with right upper bilobectomy	59.4 Gy/33 [#] 1.8 Gy per fraction
ECOG 3	Mass in anterior mediastinum and right hemithorax with solid-cystic component Abutting and displacing IVC, right atrium, SVC, ascending aorta, right PA, right hilum, and pericardium. Anteriorly mass abuts the sternum and ribs and crosses the midline Collapse right middle-lower lobes	Synovial sarcoma Mic-2, Bcl2, and focally EMA, AE1/AE3 positive S100P negative	Ifosfamide 1.8 g/m ² /day: Day 1-5 Mesna 600 mg: 0,4,8 h after ifosfamide - day 1-5 Adriamycin 60 mg/m ² Cycle every 3 weekly 6 cycles	Partial response Grade 3 anemia, thrombocytopenia, hyponatremia, Grade 4 neutropenia during 2 nd and 3 rd cycles; 75% dose for 4 th -6 th cycles	Mediastinal tumor excision with right pneumonectomy	59.4 Gy/33 [#] 1.8 Gy per fraction

PS: Performance status, ECOG: Eastern Cooperative Oncology Group, NACT: Neoadjuvant chemotherapy, PORT: Postoperative radiation therapy, SVC: Superior vena cava, IVC: Inferior vena cava, PA: Pulmonary artery, SMA: Smooth muscle actin, EMA: Epithelial membrane antigen

under 6 months follow-up and without any symptoms or disease recurrence. A summary of the patients' details is available in Table 1.

DISCUSSION

Primary mediastinal sarcoma represents 1.4% of all sarcomas and SS accounts for only 2% of all sarcomas of the mediastinum.^[1] Other common sarcomas of the mediastinum are malignant peripheral nerve sheath tumor (26%), spindle cell sarcoma (15%), leiomyosarcoma (9%), and liposarcoma (9%). There are four histologic cell types of SS: biphasic, poorly differentiated, monophasic fibrous, and monophasic epithelial.^[3] The median age of presentation is 35 years with a male predominance (2:1).^[3] Presentation of PMSS is nonspecific – chest pain, dyspnea, cough, pericardial and pleural effusion, weakness, fatigue, fever, weight loss, and superior vena cava obstruction; more than three-quarters of patients present with chest or shoulder pain with or without dyspnea.^[2,3] The most common site of metastasis is the lung followed by lymph nodes and bone.

A combination of clinicoradiological, histopathological, and immunohistochemical findings helps to establish the diagnosis of SS and to distinguish it from the other spindle cell tumors. Immunohistochemistry shows that most tumors stain positive for bcl-2 (100%) and CD99 (Mic2) (80%) with focal expression of cytokeratin and EMA.^[3] SS have chromosomal translocation t(X; 18) (p11; q11) in more than 95% of cases. In equivocal cases, demonstration of chromosomal translocation may be the only means for establishing a definitive diagnosis. Poor

prognostic risk factors include age older than 20 years, female sex, incomplete resection, tumor size >5 cm, extensive tumor necrosis, number of mitoses (>10/10 high-power fields), and neurovascular invasion.^[4] Using univariate analysis, R0-resection was the only factor associated with statistically significant improvement in survival (5-year OS = 63% vs. 0%; $P = 0.003$).^[2]

Treatment of PMSS depends on the stage of the disease, resectability, and PS of the patient. Various therapeutic strategies have been advocated including resection only, resection followed by adjuvant radiation and/or chemotherapy, incomplete resection followed by chemoradiation.^[2,3] However, there is no definite consensus about the optimum treatment modality. Moreover, a number of patients present with advanced and borderline resectable or unresectable disease (42.5%) as in our series.^[3]

Independent case reports of PMSS have been reported with treatment using different modalities.^[5-7] Patients with borderline resectable or unresectable localized disease can be treated with neoadjuvant chemotherapy (NACT) to downstage the tumor and achieve an R0-resection.^[5,6] SS is sensitive to chemotherapy with reported response rates of 30–55%. Ifosfamide-based regimens are commonly used^[8] with or without doxorubicin and appear to be associated with the highest reported objective response rate.^[9] The median time to progression for completely resected tumors is 18 months and for incomplete resection is 6 months.^[12]

All three of our patients were inoperable at presentation, with one patient in PS three. After NACT, there was partial

response in two patients and stable disease in one patient; more importantly, all three patients had considerable symptomatic improvement enabling radical, potentially curative treatment. NACT allows prehabilitation and helps selecting patients who would benefit maximum from radical surgery. All patients received adjuvant radiotherapy and under follow-up for 6 months with no recurrence. These reports suggest that patients considered inoperable may be managed by neoadjuvant therapy to achieve R0-resection followed by adjuvant radiotherapy.

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Conflicts of interest

There are no conflicts of interest.

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