ORIGINAL ARTICLE

Sarcoma of the mediastinum: case series and literature review

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KEY WORDS

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Abstract Mediastinum sarcoma is a rare tumor that represents <10% of mediastinal tumors and about 1-2% of all malignancies in general. It must be addressed in referral centers where he evaluated a multidisciplinary and multimodal management options are taken, as well as infrastructure that allows greater surgical resection and reconstruction, given the high local recurrence. We present a series of cases in 20 years of experience with the participation of several departments, fitting the definition and management with the current literature. (creativecommons.org/licenses/by-nc-nd/4.0/).

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INTRODUCTION

The mediastinum constitutes a virtual space, with potential areas for the growth of primary tumors or metastases thereof. A small group of primary tumors of the mediastinum derives from mesenchymal cells. Sarcomas are malignant solid neoplasms that account for 1% of all cancers of the body¹. Their histological classification is related to the mature mesenchymal tissue they resemble, and should not be interpreted as deriving from or originating in an organ or structure, such as mediastinal fat lipomas and liposarcomas, angiosarcomas adjacent to large vessels, rhabdomyosarcoma and leiomyosarcoma with regard to the cardiac muscle, chondrosarcoma to the ribcage and malignant pleural mesothelioma to the pleura, among others². Sarcomas affecting the thorax are mainly due to lung metastases from sarcomas originating in the limbs, most commonly in the lower extremities, sarcomas of the retroperitoneum, head and neck sarcomas and, to a lesser extent, primary thoracic sarcomas³. The latter should be considered a different entity and is classified in three groups: primary thoracic sarcomas, originating in the chest wall (ribcage wall muscles, costal arches, etc.), intrathoracic sarcomas (primary tumors of the lung or pleura) and sarcomas originating in the mediastinum (Table 1). Primary sarcomas of the mediastinum represent only 10% of tumors originating in the mediastinum. These tumors are classified as deep in the sarcoma TNM staging^{4,5}. Mediastinal tissues and structures laxity and mobility allow harboring bulky tumors, as the retroperitoneum also does^{6,7}. Given these tumors are asymptomatic at early stages, diagnostic suspicion arises by characteristic incidental radiological findings, such as pushing, shoving large lesions (generally > 7 cm) that compress neighboring structures such as the esophagus, the tracheobronchial tree, the superior vena cava, etc., and, to a lesser extent, they are infiltrating⁸⁻¹⁰. Subsequently, bulky disease favors the appearance of subtle symptoms such as dyspnea, dysphagia, dysphonia or thoracic heaviness, which guide the diagnosis. Average age at diagnosis is 40-50 years,

and the diagnosis is confirmed by histopathological report (currently, image-guided cutting-needle biopsy is the diagnostic gold standard)¹¹.

SARCOMAS OF THE MEDIASTINUM NATURAL HISTORY

Primary sarcoma of the mediastinum is defined as a mesenchymal cell tumor originating in the space between both pulmonary pleurae, and it accounts only for 10% of mediastinal tumors. Its distribution in different compartments is related to patient age, as well as to histology. In adults, 28% occur in the anterosuperior mediastinum; 11%, in the middle mediastinum; 48%, in the posterior mediastinum, and 11% involve several compartments¹². As regards histology, liposarcoma, the most common in the anterior mediastinum (38%), accounts only for 0.1-0.75% of all mediastinal tumors, which reflects the rareness of this condition. Other sarcomas of the mediastinum are Ewing's sarcoma (14%), chondrosarcoma (14%), leiomyosarcoma (14%), rhabdomyosarcoma (9.5%), angiosarcoma (4.8%), malignant fibrous histiocytoma (4.8%) and malignant peripheral nerve sheath tumor, which is the most common posterior mediastinum tumor (it accounts for 76% of all tumors originating in this compartment)¹³. As for etiology, 70% occur spontaneously and in 13% there is previous history of radiation to the chest and mediastinum, as in Hodgkin's lymphoma, and mantle field radiation, chest radiation for breast cancer, using Beck's known criteria for radio-induced sarcomas: history of radiation with latency longer than 5 years, confirmation of malignant mesenchymatous tumor at the radiated field and different histology to that of the primary tumor. In 10% of cases, there are associated hereditary syndromes such as Li-Fraumeni or Gardner's syndrome, retinoblastoma and neurofibromatosis (Von Recklinhausen disease)^{14,15} (Fig. 1).

Table 1. Classification of sarcomas that affect the thorax	
<div><div>SARCOMAS THAT AFFECT THE THORAX</div><div><div>Thoracic metastases from sarcoma</div><div><div>Primary thoracic sarcoma</div><div><div>1. Sarcomas originating in the chest wall</div><div>2. Intra-thoracic sarcomas<ul style="list-style-type: none">• Primary lung sarcoma• Mesenchymal tumor of the pleura (mesothelioma)</div><div>3. Sarcomas originating in the mediastinum</div></div></div></div></div>

Figure 1. 56-year old man with neurofibromatosis and posterior mediastinum peripheral nerve sheath tumor. He had neurofibromatosis diagnosed at adolescence with some neurofibromas, none of them larger than 6 cm or requiring previous surgical resection. The only symptom referred by the patient were paresthesias that had started 2 years prior at the zone corresponding to a T6-T7 dermatoma with increasing intensity. **A:** light brown lesions (arrow), some small-sized neurofibromas (arrowhead). **B:** non-contrasted chest CT scan: right posterior chest wall lesion shifting the lung (arrowhead) and invading the parietal pleura, originating in the nerve root corresponding to the T6 right transverse foramen (arrow). The tomography-guided biopsy reported a malignant peripheral nerve sheath tumor. The patient underwent right posterolateral thoracotomy with wide local resection with transverse foramen drilling and muscle microflap at the T6 vertebra to prevent cerebrospinal fluid fistula formation.

RADIOLOGICAL CHARACTERISTICS

Radiography and computed tomography (CT) are usually enough for diagnostic approach, both to guide percutaneous biopsy and for surgical strategy. Chest X-ray findings (Fig. 2 A) usually include mediastinal thickening or a high-density shadow. CT can distinguish a heterogeneous tumor with fat density, well-defined smooth or lobular margins and shifting of vascular, nervous and bronchial structures, with no adenopathies, teratomas and cysts^{16,17}. The sarcoma histology diagnostic presumption by CT is as high as 60% in specialized centers owing to the imaging typical characteristics (Fig. 2 B). Chest wall and vascular or nervous structures involvement are better defined by magnetic resonance imaging, as in cardiac neoplasms and posterior mediastinum tumors assessment; 75% of the latter are of neurogenic origin, mainly peripheral nerve sheath malignant tumors. In the case of a tumor confined to one hemithorax, the origin can be the posterior intercostal nerve. If the tumor crosses the midline, its origin may be found in the sympathetic trunk, which reflects the nerve roots intersection and the posterior intercostal nerves origin in the paravertebral sulcus¹⁸. As for PET-CT, it appears to be of little value, since it barely modifies the therapeutic behavior. A relationship has been found between liposarcoma histological subtypes and SUVmax. Well-differentiated liposarcoma shows a lower SUVmax (2.3 ± 1.7) than myxoid-cell, round-cell and pleomorphic liposarcoma subtypes^{19,20}. Image-guided biopsy in experienced hands is the gold standard for histological confirmation, displacing open biopsy (Fig. 3).

SURGICAL MANAGEMENT

Wide local resection with negative margins is the standard treatment for sarcomas of the mediastinum²¹. A resectable intra-thoracic sarcoma is a mesenchymal tumor originating in the lung, the pleura or the mediastinum, with no metastasis (stages I, II or III), according to the seventh edition of the AJCC staging criteria. Margin status is the main independent prognostic factor for disease-free survival (DFS) and overall survival (OR). A positive margin is defined by the presence of neoplastic cells in the section borders of the surgical specimen, and positive margin, by the absence of neoplastic cells in the section border. The latter group is divided into clearly negative margin (> 1 cm) and close to negative margin (1-10 mm)^{22,23}. Making a thorough assessment of preoperative images and patient performance status is essential, since 40% of cases are unresectable at diagnosis owing to the compromise of vital, non-reparable structures. In order for tumor resection to be carried out, 34% of patients require resection and repair of major structures. It is difficult to always achieve an optimal surgical field, and this entails little room for maneuver, since 60% of these tumors are larger than 11 cm at diagnosis. It is crucial to thoroughly know the mediastinal anatomy, the relationship of large vessels and pulmonary hilum structures and their variants for patient safety and a resection in compliance with oncologic principles²⁴. Most commonly used approaches include the clamshell incision technique, median sternotomy and anterolateral and posterolateral

Figure 2. Radiologic characteristics of a sarcoma of the anterior mediastinum. 52-year old man with progressive dyspnea over the previous 2 years. In the past few months he had experienced chest oppression and dysphagia to solid food. **A:** chest X-ray: heterogeneous lesion with opacity on both thoracic lower thirds, bilaterally. **B:** chest plain scan CT: mediastinal and pulmonary window. On the anterior mediastinum and to the right (arrowhead), a solid tumor with hypodense zones within, defined borders and no infiltration to other organs is identified; its size is larger than 21 cm in diameter and it pushes the heart to the left. Another 15-cm heterogeneous lesion (arrow) is also observed at the anterior mediastinum, which is lateralized to the left, adjacent to pericardial fat, suggestive of liposarcoma.

thoracotomy (Fig. 4-7). In special conditions, cardiopulmonary bypass and aortic counterpulsation balloon should be ready in order to achieve a R0 resection (macro and microscopic absence of neoplastic cells in the section border)²⁵. Salvage or rescue surgery is defined as surgical resection of a primary tumor of the mediastinum that is persistent or recurrent after multimodal management (chemotherapy, surgery and/or radiotherapy) with curative intention²⁶ (Fig. 8).

MULTIMODAL MANAGEMENT

Mediastinal sarcoma recurrence after surgical management is around 64% at 36 months, and OS, 50 months, even in cases where R0 resection is achieved. In patients with incomplete resection, DFS is 19 months, and OS, 24. In general terms, known factors such as age, site and size of the primary tumor do not affect DFS or OS, but histological type, degree of differentiation and resection margins do directly interfere^{4,27,28}.

So far, no significant effect of postoperative radiotherapy has been found in low grade tumors with R0 margins. Those who do benefit are the patients with R1 resections and high degree of differentiation (G3), who reach a disease and local recurrence-free survival of 28.9 months, which is close to the results attained with R0 resection. Mediastinal postoperative, conformational, tridimensional and modulated-intensity radiation modalities decrease radiotoxicity to structures, including neighboring fields^{13,29}.

Although we have established resection margin status as an independent local recurrence and overall survival prognostic factor, there is a relationship of the histolo-

gical type and degree of tumor differentiation with the response to certain cytotoxic agents. We consider synovial sarcoma, myxoid cell and round cell liposarcoma and uterine leiomyosarcoma to be chemosensitive sarcomas; pleomorphic liposarcoma, fibromyxoid sarcoma, epithelioid sarcoma, pleomorphic rhabdomyosarcoma and angiosarcoma to be moderately chemosensitive sarcomas; and alveolar sarcoma, extraskeletal chondrosarcoma and spindle-cell sarcoma to be non-chemosensitive sarcomas (Fig. 7 and 8). In the first group, preoperative chemotherapy response rates are 30-55% with ifosphamide (12 to 18 g/m²/cycle) with or without doxorubicin. The work by Italiano et al reported that neither neoadjuvant nor adjuvant chemotherapy had a significant effect on patient OS^{24,30}.

DISCUSSION

The National Institute of Cancer (INCan - *Instituto Nacional de Cancerología*) is a reference center for patients with thoracic sarcomas, which are managed mainly at the Department of Skin and Soft Tissues, where they are classified as primary tumors of the chest wall and metastatic tumors to the ribcage and multidisciplinary managed. The Department of Thoracic Oncology evaluates tumors regarded as intra-thoracic sarcomas, which in turn are classified as metastatic sarcomas to the lung and mediastinum and primary sarcomas of the mediastinum in the strict sense. We divide the mediastinum in three zones: anterior mediastinum (zone delimited by the inner surface of the sternum and the anterior surface of the large vessels), middle mediastinum (visceral compartment, limited by the pericar-

Figure 3. Mediastinal tumor diagnostic approach. **A:** CT-guided biopsy. **B, C and D:** histopathology. Hematoxylin and eosin staining and immunohistochemistry technique. Vimentin: positive. The patient referred to in figure 2 underwent tumor marker testing in order to rule out a germ-cell tumor. Lactate dehydrogenase, alpha-fetoprotein, B-human chorionic gonadotropin and carcinoembryonic antigen were negative. **A:** the patient underwent a CT-guided tru-cut biopsy. **B:** malignant neoplasm histologic section with solid growth pattern. Hematoxylin and eosin staining, 100X. Spindle cells with marked atypia are identified. **C:** immunohistochemistry, 100X: negative for smooth muscle actin. **D:** immunohistochemistry, 400X: negative in neoplastic cells for the CD34 antibody. Also negative for antibodies CD15, CD30, EMA, S-100 and MDM2. Vimentin: positive. Conclusion: intermediate-grade spindle cell sarcoma.

dial sac, which subsequently is extended up to the spinal ligament; it includes sarcomas surrounding the pericardium and heart, the trachea and main bronchi) and posterior mediastinum (it corresponds to the costovertebral region or paravertebral sulcus). When our database was carefully reviewed, for a period of 20 years and strictly adhering to the above-described definitions, sarcomas were found to represent a very small number (1.2%) of mediastinal tumors. In 95 patients with primary tumors of the mediastinum, 19 corresponded to lymphomas and 12 to tumors of the thymus. There were 50 cases of germ-cell tumors, and only 14 were primary mesenchymal tumors of the mediastinum. Out of these, 7 were tumors of the posterior mediastinum; 6 were peripheral nerve sheath tumors and one was a pleomorphic sarcoma. Among the 7 cases corresponding to sarcomas of the middle and anterior mediastinum, one had a history of non-seminomatous germ-cell tumor that was de-diffe-

rentiated to malignant fibrous histiocytoma, and there was one angiosarcoma of the right atrium, 3 liposarcomas and 2 poorly-differentiated sarcomas. Surgical control was achieved with R0 margins in 79% of cases. Only in 3 cases there was multimodal management provided, with preoperative chemotherapy and, in 2 cases, with postoperative radiotherapy. This is a very small series that doesn't allow a statistically significant analysis for conclusions about management to be drawn.

In the MSSK 50-year experience, with 47 patients diagnosed with primary sarcoma of the mediastinum, the most common histological types were peripheral nerve malignant tumor, leiomyosarcoma, liposarcoma, synovial sarcoma and malignant fibrous histiocytoma. High-grade tumors had shorter DFS and OS than low-grade tumors. R0-type resection was the most important factor for recurrence-free interval and OS (49% of survival for completely resected tumors and

Figure 4. Left posterolateral thoracotomy and wide local resection of an anterior mediastinum tumor. The patient commented in figures 2 and 3 was managed as double primary sarcoma of the mediastinum. He underwent sequential thoracotomy, initially with right posterolateral thoracotomy with wide local resection of a high-grade spindle cell sarcoma, and subsequently with left posterolateral thoracotomy (A and B) with wide local resection of a low-grade liposarcoma. C, D and E: left anterior mediastinal liposarcoma (arrowhead) not infiltrating the pulmonary parenchyma. Left superior pulmonary lobe is easily freed (arrow) by means of blunt dissection.

Figure 5. Intraoperative morphologic characteristics of the low-grade liposarcoma of the mediastinum. A: the tumor shoves but does not infiltrate the lung or mediastinal structures. B: exeresis of the surgical specimen: a 20 x 12-cm tumor is observed; its surface is smooth, well defined, with adjacent desmoplastic reaction. C and D: the snapshot and illustration show in the dotted line the change of a virtual space of the mediastinum to become a real space, generated by the tumor slow and pushing growth that allowed for it to reach the aforementioned dimensions.

18% at 3 years for incompletely resected patients. Well-differentiated liposarcoma and angiosarcoma are associated with long DFS: 60 months. Myxoid liposarcoma has a DFS of 47 months, and pleomorphic liposarcoma and dedifferentiated liposarcoma have DFS of 13 and 6 months, respectively^{13,31}.

The continuous search for control of this disease prompts patients' care in reference centers with a convergence of interdepartmental efforts that enables drawing conclusions about management, which is only achieved through long periods of collection of patients and close surveillance, given the rareness of this condition.

Figure 6. Imaging correlation and macroscopic appearance of a synchronous double sarcoma of the mediastinum. At right, high-grade spindle-cell sarcoma. On the left, low-grade liposarcoma. Continuing the analytical sequence of previous figures' case, on CT scan (A), the heterogeneous density and irregular borders of the lesion at right (arrowhead) are related to spindle-cell sarcoma characteristic macroscopic appearance. B: external surface of the tumor, with irregular borders, opaque yellow-colored and partially covered with adipose tissue. C: on the section surface, hemorrhagic and cystic areas are observed. Again, the arrow on the CT image (A) points at the homogeneously hypodense appearance of a liposarcoma at the left side of the mediastinum. D: product of a 22 x 14 x 6 cm left mediastinal tumor resection. The external surface of the tumor looks congestive, smooth and has irregular borders. E: at the section area, the surgical specimen is yellow-colored, smooth and shiny, and the lipomatous appearance of the tumor is evident.

Figure 7. Histology. Staining with hematoxylin and eosin. High-grade spindle-cell sarcoma and low-grade synchronous anterior mediastinum liposarcoma. F: Histological section with high-grade malignant pleomorphic neoplasm. Staining with hematoxylin and eosin, 100X. G: at higher magnification (400X), cells with accentuated pleomorphism and cytological atypia are identified. H: at some areas of the field, tumor-type multinucleated giant cells. I: coexistence of soft muscle areas, adipose cells with atypia and multinucleated giant cells is observed. Conclusion: high-grade spindle-cell sarcoma. J: well-differentiated malignant neoplasm made up of adipose tissue. K: adipose tissue, separated by bands of connective tissue, is observed. Staining with hematoxylin and eosin, 100X. L and M: adipocytes without atypia. Staining with H and E, 400X. Conclusion: low-grade well-differentiated liposarcoma.

Figure 8. Recurrent angiosarcoma of the right atrium in a 37-year old man. “Bench” surgery. Resection of the right atrium tumor from the heart to the operating table. 37-year old man with an anterior and middle mediastinum sarcoma with pericardial infiltration, respecting the right cavoatrial junction. Following induction chemotherapy management with partial response, the patient underwent wide local resection by sternotomy. During his follow-up, at 39 months, he experienced recurrence at right atrium. The patient underwent salvage surgery by means of median sternotomy, placement of a cardiopulmonary bypass pump and wide local resection, which, in order to obtain negative margins, required the resection of the right atrium and reconstruction with a bovine pericardium graft by means of “bench” surgery and cardiac autotransplantation. A and B: approach by means of median sternotomy. C and D: tent-shaped exposure of the pericardial sac operating field. C: cardiopulmonary bypass pump system. F and G: tumor resection with margin on right atrium. H: tumor exeresis. I: right atrium reconstruction with bovine pericardium graft.

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