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Mediastinal Liposarcoma: Case Report and Literature Review

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Abstract

Liposarcomas (LS) are the second most common type of soft tissue malignancies in adults; they arise from mesenchymal cells and account for 1% of all adult cancers and 15% of all pediatric cancers. The site of origin can be from anywhere there is fat in the human body. LS are classified based on the primary site of origin, and mediastinal LS are extremely rare. When mediastinal neoplasms are stratified based on histology, they represent less than 1% of all mediastinal tumors. To date, less than 150 cases have been reported in the English literature. This article aims to present an unusual case of an extremely rare malignancy and perform a systematic review of the latest literature. In this report, our group is documenting the presentation, management, and outcome of a 65-year-old male patient with a massive anterior mediastinal primary LS. The tumor was displacing the mediastinum into the right chest, occupying most of the left chest, and pushing the diaphragm into the abdomen. Mediastinal liposarcomas are extremely rare malignancies and can prove to be challenging to diagnose and treat. Aggressive surgical treatment with R0 resection is the gold standard, however, tumor biology in many cases is associated with variable growth rates and encroachment of adjacent vital structures and blood vessels. When complex anatomical structures preclude an R0 resection, there is a high incidence of local recurrence. In cases where there is a high risk of recurrence, radiotherapy is indicated and chemotherapy has a more limited role.

Keywords

Liposarcoma (LS), Well-Differentiated Liposarcoma (WDLS), Dedifferentiated Liposarcoma (DDLS)

1. Introduction

The 2012 National Comprehensive Cancer Network (NCCN) liposarcomas classification, groups them histologically as: "well-differentiated liposarcomas" (WDLS), "myxoid," "pleomorphic," and "dedifferentiated liposarcomas" (DDLS) [1]. When this neoplasm arises from the mediastinum, the dedifferentiated type has a poorer prognosis than the well-differentiated type [1].

Overall, LS are the second most common type of soft tissue malignancy in adults, [2] they occur predominantly in the lower extremities and retroperitoneum.

The well-differentiated is the most common type of LS, and it is further subclassified into three subtypes: lipoma-like, sclerosing, and inflammatory [2]. The well-differentiated LS is a well-circumscribed mesenchymal tumor that arises from adipose tissue [2]. Primary mediastinal LS are extremely rare, accounting for less than 1% of mediastinal tumors and 2% of LS [3] [4]; thus, only a small number of cases have been reported [1].

This article describes the initial multidisciplinary management of a 30 cm anterior, superior mediastinal well-differentiated LS. At the time of the initial encounter, the massive tumor was occupying the entire left thoracic cavity, displacing the diaphragm inferiorly, the heart, and the mediastinum to the right of the midline. We also describe the follow-up and a second operative procedure associated with a subsequent histologic transformation from a WDLS to a DDLS.

2. Case Report

A 65-year-old male patient was initially diagnosed with prostate cancer several months before the mediastinal liposarcoma was detected. His initial presenting symptoms included modest abdominal pain and shortness of breath with minimal exertion that became progressively worse in the previous month. The initial staging for prostate cancer included a CT scan of the abdomen and pelvis in which a left upper quadrant mass was described. A subsequent PET/CT described a large heterogeneous mass with fatty, solid, and cystic components occupying the entire left thorax, displacing the diaphragm inferiorly and the heart and mediastinum to the right of the midline. Reported findings of multiple localized areas with increased metabolic activity were consistent with a pleomorphic liposarcoma. Other findings included; a partial compressive collapse of the left lung with tracheal and esophageal deviation to the right hemithorax and extension of the tumor's apex through the retro clavicular space into the left side of the neck. The tumor encroached the aortic arch, the left common carotid and the left subclavian vein. This massive tumor was compressing the left pulmonary vessels (**Figures 1-3**).

For the management of this massive neoplasm, a surgical team of thoracic surgery, complex surgical oncology, and anesthesia planned an operative procedure.

The patient underwent a radical resection of the mediastinal liposarcoma oc-

cupying the left thorax and left neck. The procedure was done through a left thoracotomy with an "H" incision (4th and seventh intercostal incisions and a vertical rib transection connecting both intercostal incisions).

The tumor was pushing the diaphragm down into the abdominal cavity, and it looked as if the tumor was originating from the retroperitoneum. However, there was no evidence of the tumor going through the diaphragm into the peritoneal cavity. The left chest's initial exploration identified the tumor originating in the mediastinum and extending superiorly into the left neck. A decision was made to first deal with the tumor extension into the neck.

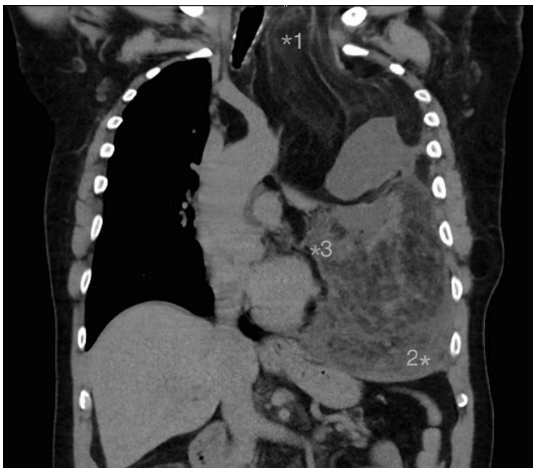

Figure 1. 1—Tumor extending to the neck; 2—Tumor pushing the left hemidiaphragm into the abdomen; 3—Tumor pushing the heart and mediastinum to the right midline.

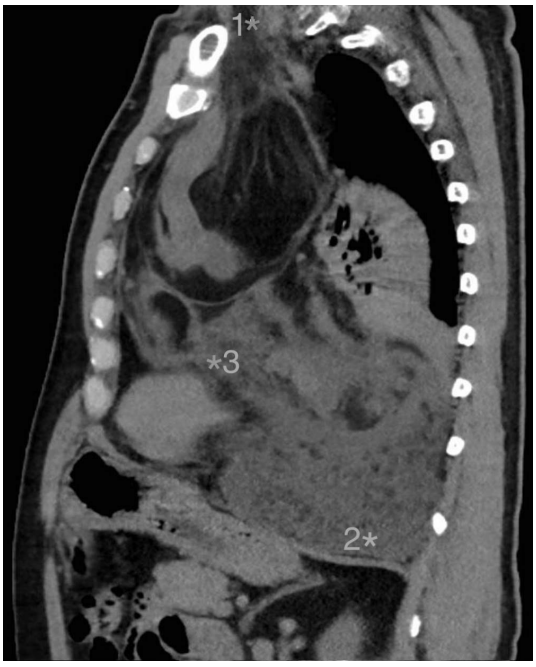

Figure 2. Lateral view. 1—Tumor extending to the neck; 2—Tumor pushing the left hemidiaphragm into the abdomen; 3—Tumor pushing the heart and mediastinum to the right midline.

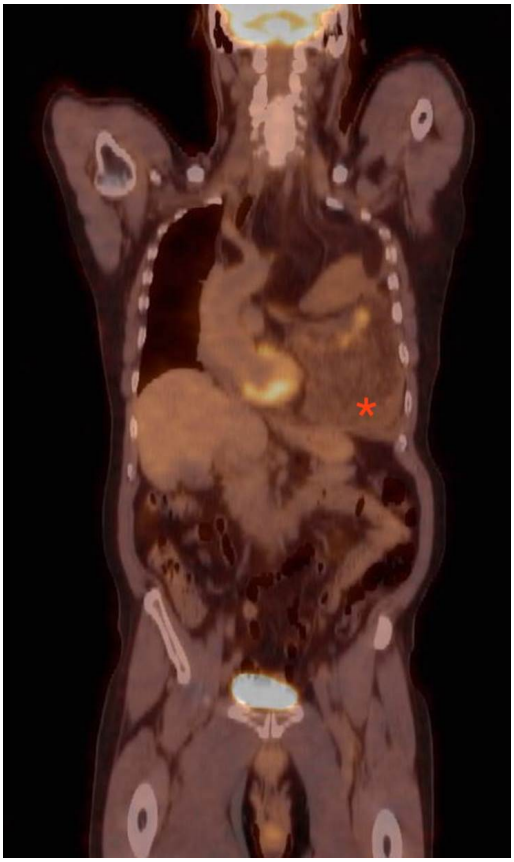

Figure 3. PET-CT.

We used a cervical incision, which extended from the suprasternal notch to the mastoid process, along the posterior border of the sternocleidomastoid muscle to excise the tumor extension into the left neck.

The tumor was extending superiorly up to level three of the cervical lymph nodes. The lymph nodes from the posterior jugular chain at levels 3 and 4 were dissected from the internal jugular vein and common carotid artery and incorporated into the tumor's en-block resection encroaching them. Additional dissection was required at the thoracic outlet level, where the tumor was separated from the right subclavian vein and artery and then transected at this level. The specimen removed from the neck measured 15 × 10 cm (**Figure 4**). The bulkiest part of the tumor rested in the lower chest, where it was encroaching the phrenic nerve, which could not be preserved. The tumor was then separated from the pericardium, the left mainstream bronchus, and the left pulmonary vein. This specimen also represented only a partial resection, and when removed from the mediastinum and left chest, it measured 30 × 20 cm. (**Figure 5**). The debulking continued by removing the tumor from the thoracic inlet, the innominate vein, and the artery. Once this last portion of the tumor was removed, it measured 10 × 15 cm. The decision to stop the dissection was made since the recurrent laryngeal nerves and the phrenic nerves were not identified. The entire procedure managed to excise approximately 95% of the tumor (**Figure 6** and **Figure 7**).

Histological examination revealed a well-differentiated liposarcoma with sclerotic regions and mature smooth muscle (Figure 8 and Figure 9) with a mitotic rate of 0 - 1/10 high-power field (HPF). According to the World Health Organization (WHO) classification of soft tissue tumors, this was further classified as a grade II.

The patient had an uneventful hospital stay before being discharged on post-operative day 10.

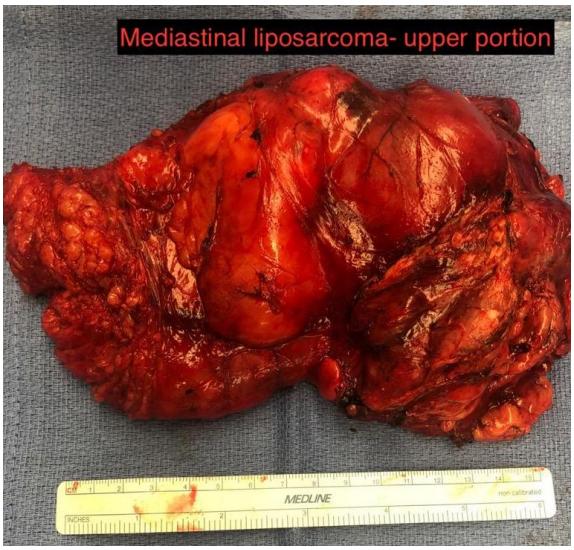

Figure 4. Mediastinal liposarcoma-upper portion.

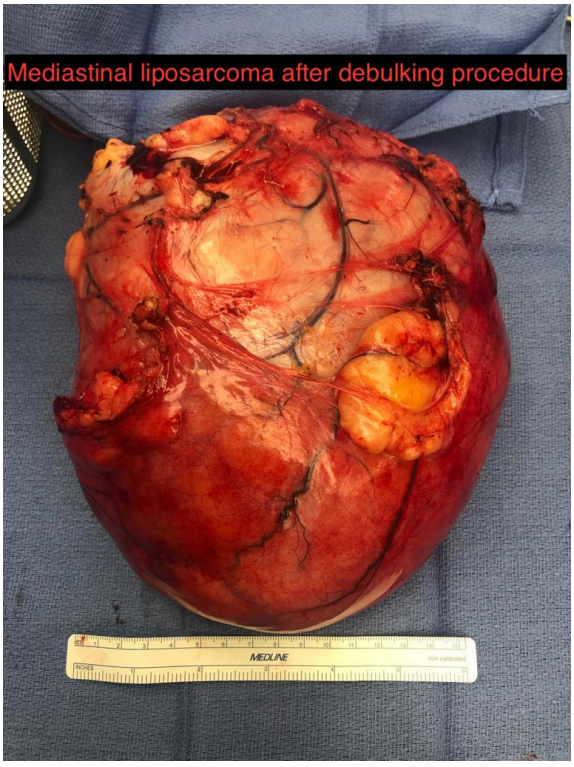

Figure 5. Mediastinal liposarcoma after debulking prodedure.

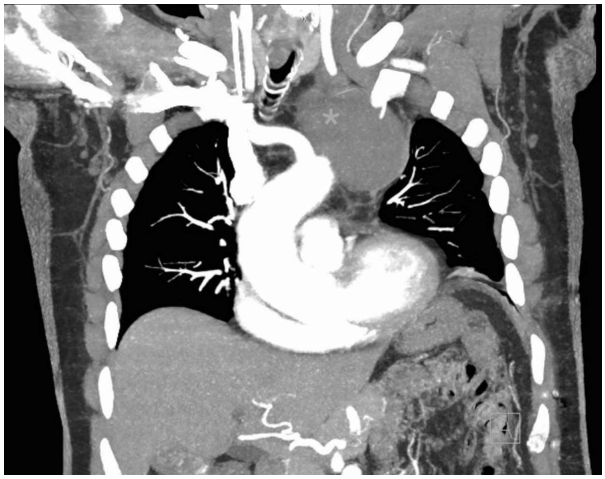

Figure 6. Residual tumor pushing the trachea to the right midline and wrapped around the aortic arch.

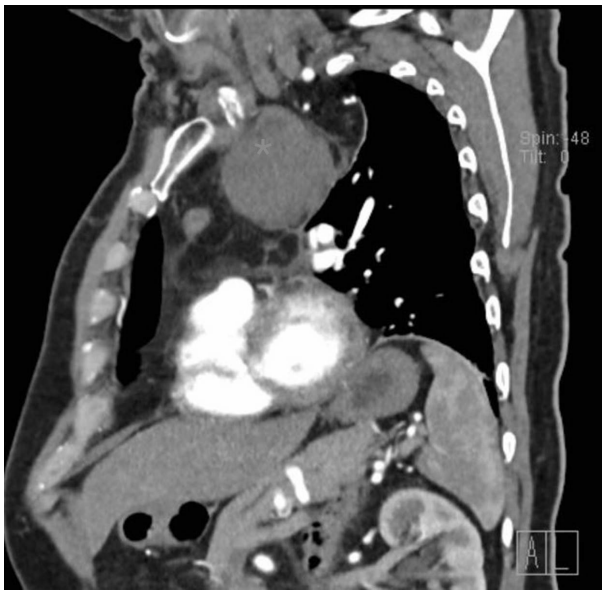

Figure 7. Lateral view of residual tumor.

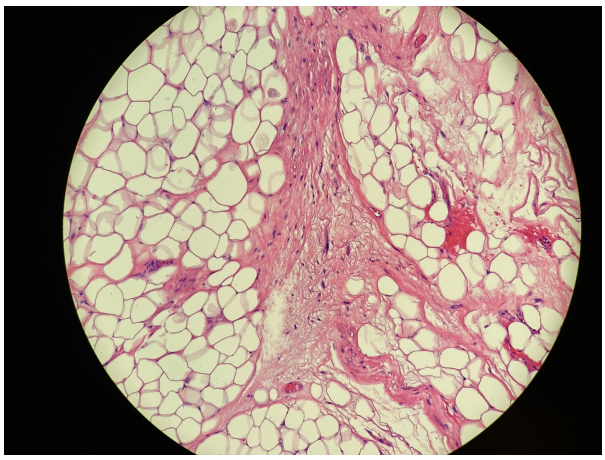

Figure 8. Areas of well-differentiated liposarcoma.

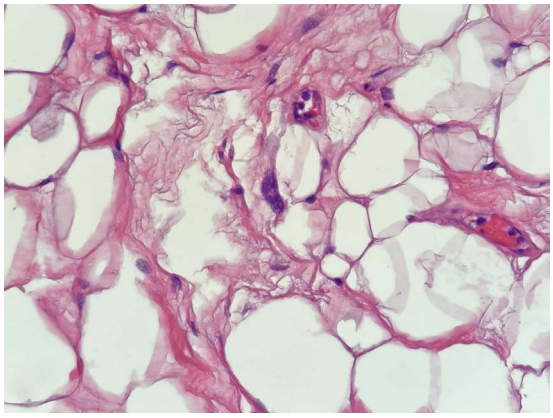

Figure 9. Areas of well-differentiated liposarcoma.

The patient was then seen at the 30-day follow-up visit, where the surgical wound had healed well (**Figure 10**).

A follow-up CTA scan taken ten months after the initial surgery described a 9.1 × 4.2 × 7.2 cm persistent mass in the superior mediastinum, anterior to the great vessels, consistent with a persistent mediastinal liposarcoma. With these findings, we decided to bring the patient back to the operating room for an RO resection with curative intent.

After performing a medial sternotomy, the tumor's dissection started at the level of the inferior extension of the tumor covering the arch of the aorta, the root of the innominate artery, and the origin of the left common carotid and left subclavian arteries. The dissection of the innominate vein was completed using blunt and vessel sealing bipolar energy. Separation of the tumor from the anterior chest wall was achieved with the same technique; first on the right side, then on the left side, and subsequently at the superior's most extension of the tumor into the neck behind the clavicles' head. During the deep portion of the tumor's dissection extending to the posterior mediastinum along the aortic arch, the innominate artery was perforated. Once the repair of the innominate artery was completed, the dissection of the tumor was finalized. A small portion of the tumor invading the innominate artery could not be separated from the innominate artery perforation site.

The histological examination revealed a DDLPS, consisting of WDLS (50%) and DDLS with homologous and heterologous elements (Rhabdomyosarcomatous differentiation, 50%) with a mitotic rate of 0/10 HPF's (**Figure 11** and **Figure 12**) that were positive for Desmin in IHC stain (**Figure 13**) and MDM2 + (murine double minute-2) on IHC stain (**Figure 14**). Grade 1 out three according to the French "Federation Nationale des Centres de Lutte Contre le Cancer" (FNCLCC) system. The pathological staging for sarcomas in the mediastinum is staged akin to those arising from the retroperitoneum; therefore, this tumor's designation was a T3. The patient had an uneventful hospital stay before being discharged on postoperative day 4. The patient was referred to radiation and medical oncology for consideration of adjuvant radiotherapy and targeted therapy. He completed 32 cycles of external beam radiotherapy with a total dose of

6400 cGy an received four cycles of adjuvant chemotherapy with Doxorubicin and Dacarbazine that were well tolerated. His last CT scan from 02/10/2021 showed a complete response with no evidence of recurrence. We will continue to follow up with the patient every 3 months.

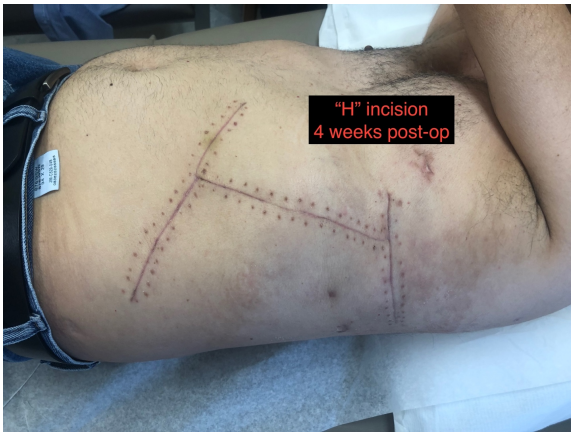

Figure 10. "H" Incision 4 weeks post-op.

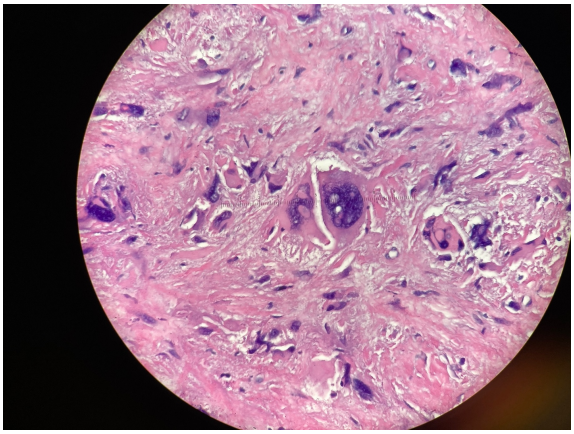

Figure 11. Areas of de-differentiated liposarcoma with Rhabdomyosarcomatous differentiation.

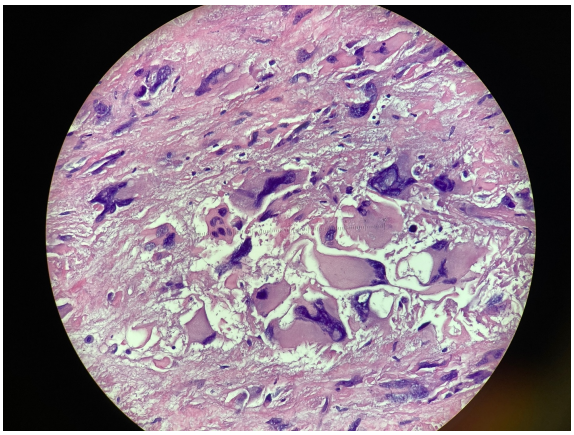

Figure 12. Areas of de-differentiated liposarcoma with Rhabdomyosarcomatous differentiation.

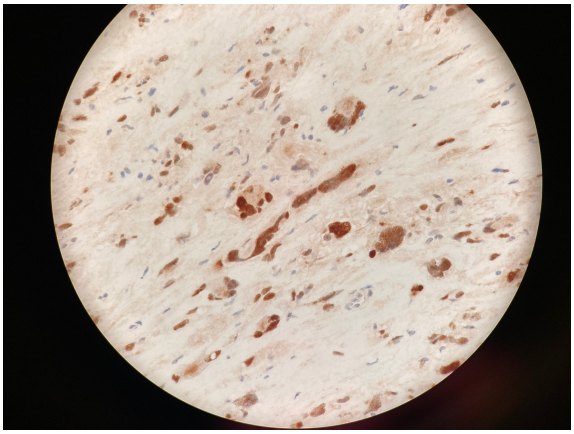

Figure 13. Desmin (+) IHC stain.

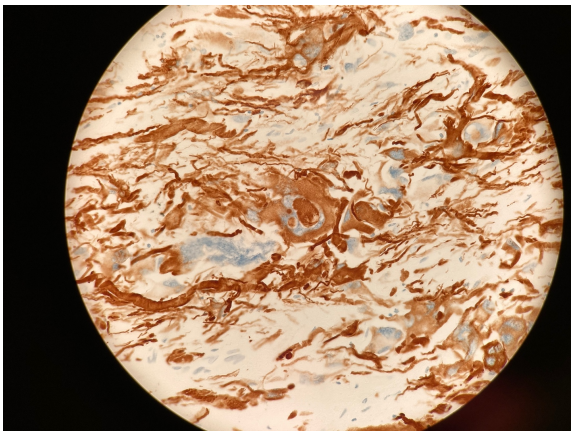

Figure 14. MDM2 (+) IHC stain.

3. Discussion

All patients with suspected LS should be evaluated and treated by a multidisciplinary sarcoma team. Best practices guidelines, and the histologic diversity of LS, dictate the need for a team with expertise in managing these neoplasms. Such a team should include a sarcoma pathologist, a medical oncologist, a radiation oncologist, a radiologist, and an experienced sarcoma surgeon. Multidisciplinary treatment planning allows for effective and efficient multimodality patient care. The multidisciplinary sarcoma team approach has improved clinical outcomes in multiple studies in Europe and the United States. In one study of 375 patients with extremites and retroperitoneal sarcomas that were not treated at a specialized center had a 2.4-fold higher risk of local recurrence compared to those treated by a multidisciplinary sarcoma program [5]. Despite having a multidisciplinary approach, patients tend to have a poor prognosis due to tumor locations making it challenging to reach R0 resection.

Surgery is the only curative treatment for LS; however, multimodal therapy is often indicated for large, high-grade histologic subtypes or recurrent and metastatic disease. The treatment of choice for primary liposarcoma is resection with negative margins, regardless of the subtype, whenever possible. Due to the pauc-

ity of cases, the clinicopathological features and treatment outcomes de guidelines for the management of primary mediastinal dedifferentiated liposarcoma remain poorly established.

Many sarcoma experts recommend preoperative core needle biopsy to establish the LS type and better plan the medical decision-making. In this particular case, a decision was made to proceed with surgery without a preoperative tissue sample, primarily due to the lack of clear benefit of establishing a preoperative histologic diagnosis. Because of the relatively indolent nature of WDLS, all tumors, regardless of size, can be treated with surgery alone. Once again, in this case, there was no apparent benefit of preoperative radiotherapy, chemotherapy, or targeted therapy.

Patients with a WDLS who are managed with radical surgery are reported to have the best prognosis [6]. Radiation therapy for LS is reserved for recurrent disease or incomplete resections. In this particular case, after the patient initially refused postoperative radiation therapy, we planned for a staged resection, the timing of which was determined by the physical, physiological, and emotional recovery of the patient. Another factor that was taken into account for the planned second surgical procedure was tumor behavior determined by serial chest CT scans.

For DDLS, adjuvant radiation therapy is indicated for tumors greater than 5 cm. Chemotherapy or targeted therapy is rarely used for DDLS of the extremities or retroperitoneum unless there is unresectable or metastatic disease.

LS compromises approximately 1% of all malignancies [4], and it is the most common soft tissue sarcoma, accounting for 20% - 30% of soft tissue sarcomas in adults [7]. Mediastinal liposarcoma is a very rare primary malignant tumor; it accounts for only 0.1% to 0.75% of all mediastinal tumors [2] [4]. This tumor's behavior in the mediastinum resembles to its behavior in the lower extremities and the retro-peritoneum, the most common sites, respectively [4] [7]. These are poorly circumscribed tumors that grow slowly and tend to involve adjacent organs early by direct extension. The laxity and mobility of the tissues and the mediastinal structures allow for gradual adaptation of these structures in accommodating slow-growing tumors, that in this case reached a massive size. This biological behavior explains why the patients are often asymptomatic and become symptomatic only when the tumors invade or compress vital organs and structures. [4] [8]

The well-differentiated liposarcoma, also known as an atypical lipomatous tumor, is the most common type of LS. It has histologic features that in many areas resemble mature adipose tissue and can be further sub-classified in lipoma-like, sclerotic, and inflammatory [1] [2] [7]. The survival rate in patients with dedifferentiated or pleomorphic liposarcomas is significantly shorter than in patients with myxoid or well-differentiated liposarcomas [1] [9]. Well-differentiated and dedifferentiated liposarcomas carry amplification of the MDM2 and CDK4 cell cycle oncogenes with protein overexpression and can also overexpress the cell cycle regulator p16. The addition of immunohistochemistry for

the MDM2, CDK4, and p16 to the histologic diagnosis has been shown to help distinguish this group of tumors from other adipocytic neoplasms in their differential diagnosis. Mediastinal liposarcoma develops more commonly in the posterior mediastinum in about 48% of the cases, followed by 28% in the anterior-superior mediastinum, 11% in the middle mediastinum, and 11% affecting various sites [4] [8]. Mediastinal liposarcoma tends to have a slow growth; therefore, it may remain asymptomatic for a long time until it grows in size and starts becoming symptomatic due to direct invasion or compression of adjacent structures such as the heart, great vessels, or lungs (1, 4). The compression of adjacent structures can cause dysphagia, dyspnea, cough, superior vena cava syndrome, Horner's syndrome, spinal nerve paralysis, tachycardia, and heart failure [2].

Regarding the etiology, 70% are spontaneous, 13% have a history of chest and mediastinal radiation, such as Hodgkin's lymphoma or a previous history of any chest cancer treated with radiation. About 10% may also have associated hereditary syndromes, such as Li-Fraumeni, Gardner syndrome, retinoblastoma, and neurofibromatosis type 1 [8] [9].

Local recurrence or distant metastasis can occur years after the primary tumor was removed [3]. Delayed de-differentiation can also occur; this is why long-term surveillance of the surgical site is recommended [7]. This type of tumor should be treated in centers where all involved specialties are available, and with infrastructure optimized for complex surgical resection and reconstruction. A follow-up and post-treatment monitoring protocol needs to be well outlined due to the 30% rate of local recurrence [8]. Our follow-up protocol establishes a physical exam every 3 months with basic blood work, MRI of the neck and chest every six months to minimize diagnostic radiation, and PET/CT once a year.

According to the staging criteria from the 7th edition of the America's Joint Committee on Cancer (AJCC), a resectable intrathoracic sarcoma is a mesenchymal tumor that arises in the lung, pleura, or mediastinum and it is not yet metastatic (stage I, II or III) [3] [8]. Margin status is the foremost independent prognostic factor for disease-free survival (DFS) and overall survival (OS).

A thorough evaluation of the preoperative images and the patient's functional status is essential since 40% of cases are unresectable at the time of diagnosis due to the direct involvement of non-repairable vital structures [7] [8]. About 34% of patients will require reconstruction of larger structures to resect the tumor, and in 60% of the cases, tumors that are larger than 11 cm at the time of diagnosis make the surgical approach difficult with a narrow margin of maneuver. The most commonly used approaches are Clamshell incision, median sternotomy, anterolateral and posterolateral thoracotomy [7] [8].

A median sternotomy is a common approach to resecting mediastinal tumors, but it does not allow adequate exposure of mediastinal tumors with thoracic cavity extension. The Clamshell incisions are used to resect bilateral pulmonary metastases, large mediastinal tumors, and bilateral lung transplantation. Because a component of Clamshell incisions is a sizeable transverse incision, they provide adequate access to the intrapleural space bilaterally. In contrast, the median

vertical incision for sternotomy provides better exposure to superior and anterior mediastinal lesions [6] [7]. Surgical removal is the treatment of choice for mediastinal liposarcoma. If the entire tumor cannot be resected, surgical debulking will result in symptomatic relief. Radiotherapy and chemotherapy may be added as adjuncts to surgery, although liposarcomas seem to have low sensitivity [2] [4].

Recurrence is common in liposarcomas, and it becomes apparent within the first six months after the initial therapy, but it may be delayed for 5 or 10 years following the initial excision [4]. Recurrence is related to the incomplete excision and tumor tissue left behind at the time of surgery. For this reason, a close follow-up is needed [4].

More recent data suggests that immunologic agents in the frontier might help in the near future.

4. Conclusion

The continuous search for control of this disease motivates patients' attention in referral centers, combined with multi-specialties efforts that allow management conclusions, which is only achieved through long periods of patient data collection and close surveillance and follow-up, given the rarity of this tumor. Mediastinal liposarcoma can prove to be a diagnostic and treatment challenge, and aggressive treatment with surgical resection should be initially considered to achieve better outcomes.

Author Contributions

Idea and manuscript elaboration: Adrian Legaspi, M.D., Jeronimo Garcialopez De Llano, M.D., Maria Fernanda Mijares, M.D. Manuscript evaluation and review: Adrian Legaspi, M.D., Vanitha Vasudevan, M.D., Amit Sastry, M.D. Rodrigo Arrangoiz, M.D, Frank De la Cruz, M.D, Jennifer Fernandez Garcia, M.D.

Consent

Record release and authorization to use and disclose health information was signed by the patient on 2/25/2021.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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