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Primary mediastinal dedifferentiated liposarcoma: Five case reports and a review

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Abstract

Background: Liposarcoma has been subclassified histologically into well-differentiated, myxoid, pleomorphic, and dedifferentiated types. The dedifferentiated type generally shows poorer prognosis than the well-differentiated type. Because of its rarity, the clinicopathological features and clinical outcomes of primary mediastinal dedifferentiated liposarcoma remain unclear.

Methods: Five patients with primary mediastinal dedifferentiated liposarcoma were treated at Shinshu University Hospital between January 2012 and August 2017. We investigated the clinical characteristics, including age, gender, radiographic findings, pathological status, and clinical and treatment outcomes.

Results: Four of the five patients initially underwent radical surgical resection. One patient was disease-free after surgery, but the remaining three patients developed local recurrence in the mediastinum after surgical resection. Two of these patients underwent repeat surgical resection, resulting in long survival (60 and 40 months, respectively), while the other underwent proton beam therapy and showed no evidence of recurrence as of 17 months after treatment. The remaining patient was treated with chemotherapy using doxorubicin because of advanced inoperable disease, but failed to show a response and died within a month of the initiation of chemotherapy. Although the maximum standardized uptake values on fluorodeoxyglucose-computed tomography were relatively low, there was a slight positive relation between these values and the Ki-67-positive ratio in the tumor.

Conclusion: Aggressive treatment by surgical resection should be considered for mediastinal dedifferentiated liposarcoma, even in cases with local recurrence.

Introduction

Liposarcoma commonly occurs in the retroperitoneum or thigh, while primary mediastinal liposarcoma is rare and only a few cases have been reported to date.[1–9] Liposarcoma has been subclassified histologically into well-differentiated, myxoid, pleomorphic, and dedifferentiated types according to the 2012 National Comprehensive Cancer Network classification of liposarcoma.[6] Chen *et al.* reported that the dedifferentiated type has poorer prognosis than the well-differentiated type in intrathoracic liposarcoma, including lesions of lung, pleura, or mediastinum origin.[6] However, the clinicopathological characteristics of dedifferentiated liposarcoma remain unclear because of its rarity, especially when originating from the mediastinum. We encountered five cases of primary mediastinal dedifferentiated liposarcoma in our institute. Herein, we summarize the clinicopathological characteristics and outcomes of our cases, and conduct a review of the relevant literature.

Methods

Patients

The data of five patients with mediastinal dedifferentiated liposarcoma treated at Shinshu University Hospital between January 2012 and August 2017 were included in this study.

We investigated patient characteristics, including age, gender, tumor characteristics, pathological status, and outcomes. During follow-up, chest computed tomography (CT) was performed at least once every six months. Overall survival (OS) was defined as the interval from initial surgery or the commencement of chemotherapy to death or the last follow-up date (September 2017). Recurrence-free survival (RFS) was calculated from the date of surgery to the date of recurrence.

The institutional research ethics committee approved the study (No. 3395, Shinshu University School of Medicine).

Literature review

We searched the PubMed database for studies published between 2002 and 2016 using the keywords: dedifferentiated liposarcoma, mediastinum, or mediastinal.

Results

Case presentations

Case 1

A 45-year-old-woman visited our hospital after an abnormality was detected on chest CT screening. She had no symptoms and no past history. The chest CT scan showed a tumor measuring 121 × 82 × 58 mm extending from the cervical region to the middle mediastinum with homogenous low density (Fig 1a). Fluoro-2-deoxyglucose positron emission tomography (FDG-PET)-CT revealed positive accumulation (maximum standardized uptake value [SUVmax] 1.93). Surgical resection via the cervical approach was performed followed by video-assisted thoracic surgery (VATS) on the right side. The tumor was completely resected and the patient had an uncomplicated postoperative course. A diagnosis of dedifferentiated liposarcoma was made, and Ki-67 immunostaining was < 10%. Chest CT showed solitary local recurrence in the middle mediastinum 51 months after surgical resection (Fig 1b). As no other recurrent lesions were detected on FDG-PET-CT, repeat surgical resection was performed by right-side thoracotomy. The pathological findings of the resected tumor were the same as those of the primary tumor. Although adjuvant therapy was not performed, the patient has shown no signs of recurrence 12 months after repeat surgery.

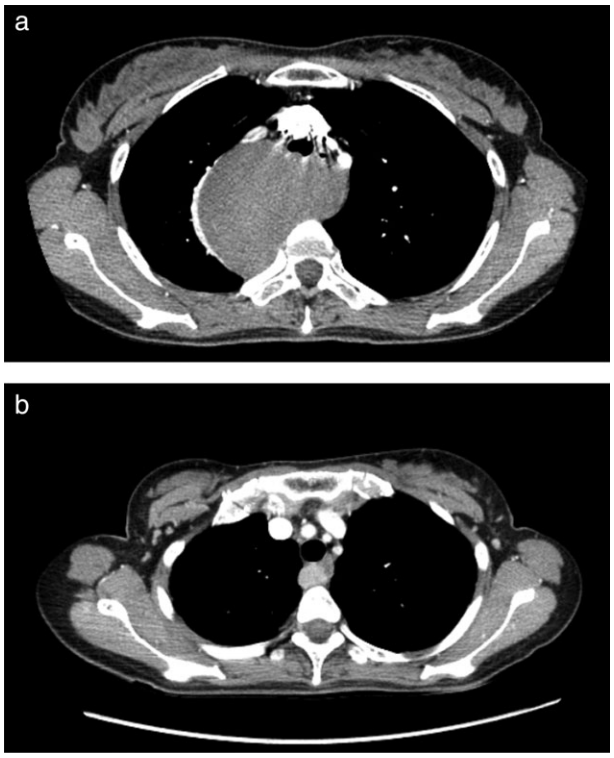

Figure 1 Chest computed tomography scans in Case 1 (**a**) preoperatively and (**b**) at recurrence. A 121 × 82 × 58 mm tumor was observed extending from the cervical region to the middle mediastinum with homogenous low density. Solitary local recurrence was observed in the middle mediastinum 51 months after surgery.

Case 2

A 62-year-old woman with no symptoms visited our hospital after an abnormality was detected on CT screening. Chest CT showed a tumor measuring 66 × 88 mm in the middle mediastinum with homogenous density (Fig 2a). FDG-PET-CT revealed positive accumulation (SUVmax 2.5); mediastinal liposarcoma was suspected based on the radiographic findings. Surgical resection was performed via median sternotomy, and as much tumor and peripheral fat tissue were resected as possible. Histopathologically, the tumor was diagnosed as dedifferentiated liposarcoma. Ki-67 immunostaining was approximately 20%. Adjuvant therapy was not performed. After 28 months, tumor recurrence was detected on chest CT (Fig 2b), and proton beam therapy was performed. No evidence of recurrence has been observed as of 17 months after radiotherapy.

Case 3

An 81-year-old man with an anterior mediastinum tumor detected on chest CT during follow-up of autoimmune

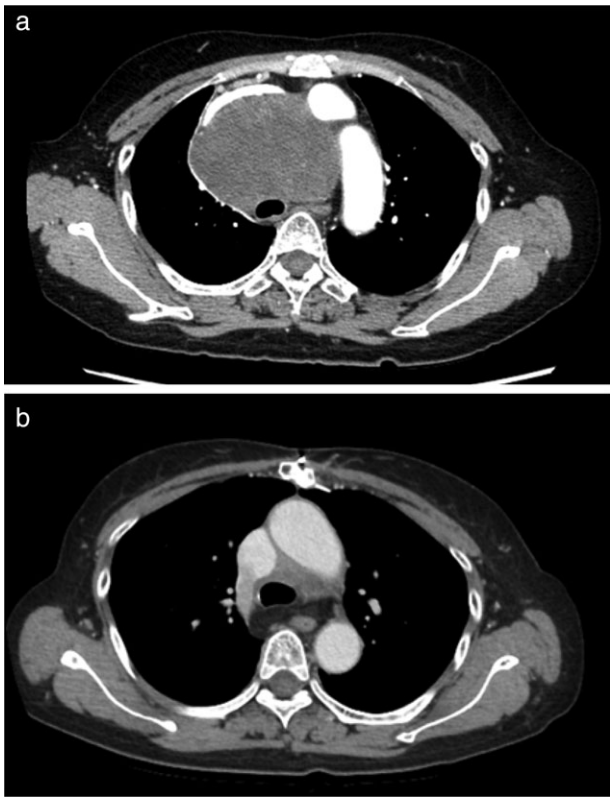

Figure 2 Chest computed tomography scans in Case 2 (**a**) preoperatively and (**b**) at recurrence. A 66 × 88 mm tumor was observed in the middle mediastinum with homogenous density. Tumor recurrence was detected in the posterior mediastinum after 28 months.

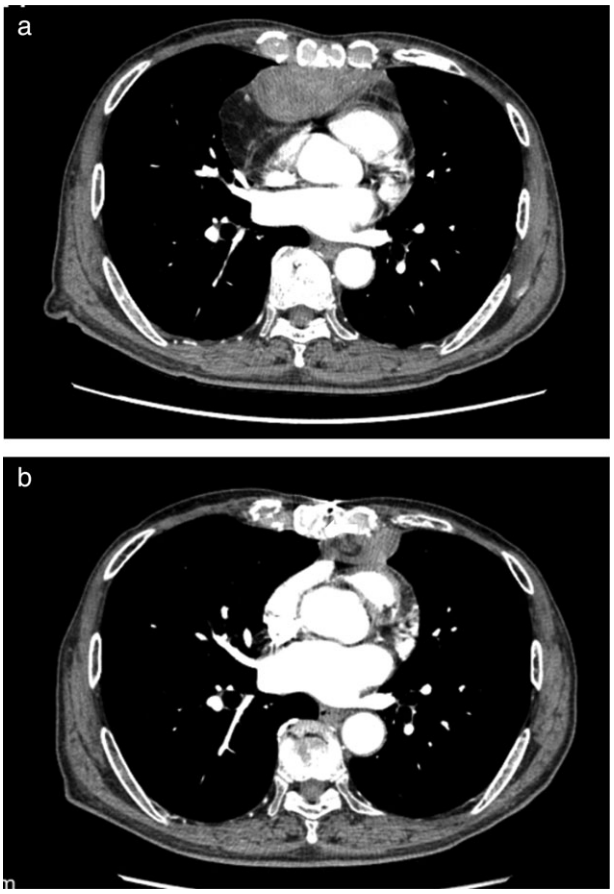

Figure 3 Chest computed tomography (CT) scans in Case 3 (**a**) preoperatively and (**b**) at recurrence. A 66 × 30 mm tumor was observed in the anterior mediastinum, which had heterogeneous areas of low and high density. After 28 months, follow-up chest CT showed recurrent tumors behind the sternum.

pancreatitis was referred to our hospital. Chest CT showed a tumor measuring 66 × 30 mm in the anterior mediastinum, with heterogeneous low and high-density components (Fig 3a). FDG-PET-CT revealed positive accumulation in the solid component (SUVmax 9.2) and anterior mediastinal liposarcoma was suspected. Sternotomy was performed and the tumor was completely resected without composite resection of other great vessels or organs. The resected tumor was diagnosed as dedifferentiated liposarcoma. Atypical cells were detected in the peripheral fat tissue, which showed low density on chest CT. The positive ratio of Ki-67 immunostaining was 50%. After 28 months, follow-up chest CT showed recurrent tumors behind the sternum. Repeat surgical resection was performed, but local recurrence was observed after eight months (Fig 3b). Radiotherapy was performed and the disease was well controlled.

Typical pathological and immunohistological findings are shown in ***Figure 4. Hematoxylin and eosin staining in case 3 revealed spindle tumor cells proliferate with fibrous stroma. Immunohistochemical analysis was positive for CKD4 and slightly positive for MDM2.

Case 4

A 75-year-old man visited our hospital after an abnormal shadow was detected on chest X-ray screening. He did not exhibit any symptoms but chest CT showed a huge tumor in the posterior mediastinum projecting on either side of the intrathoracic space (Fig 5). The esophagus was surrounded by the tumor. The tumor was suspected to be mediastinal liposarcoma and radical surgical resection was performed by bilateral thoracotomy. First, left-side complete VATS was performed. The tumor was smooth with only mild adhesion between the tumor and lung, aorta, and diaphragm. Leaving only adhesion around the esophagus, surgery was performed on the right side with a 20 cm post lateral incision. Like the left side, the extent of adhesion between the tumor and surrounding tissue was minimal. The tumor surrounded the esophagus, as determined on preoperative chest CT. However, there was no invasion of the esophagus, and it was relatively easy to peel the

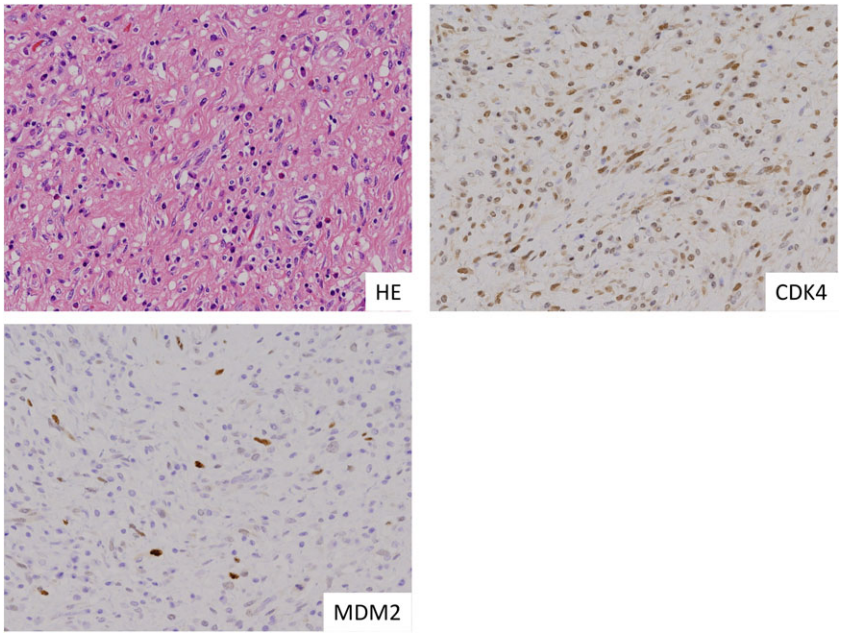

Figure 4 Histopathological findings in Case 3. Hematoxylin and eosin staining revealed spindle tumor cells proliferate with fibrous stroma. Immunohistochemical analysis was positive for CDK4 and slightly positive for MDM2.

tumor off the esophagus. The tumor was removed en bloc and complete resection was performed. The tumor was diagnosed as dedifferentiated liposarcoma and the rate of positive Ki-67 immunostaining was 3%. Chest CT has shown no recurrence in three months.

Case 5

A 78-year-old man visited our hospital because of rapidly progressing hoarseness and dyspnea over a three-month period. Chest CT showed a giant tumor in the middle and posterior mediastinum extensively surrounding the trachea (Fig 6). As radiographic findings were suspicious for mediastinal liposarcoma, chemotherapy with doxorubicin (60 mg/m^2) was immediately commenced. However, it was not effective and he died two weeks later as a result of respiratory failure. Post-mortem pathological examination revealed that the tumor was dedifferentiated liposarcoma but had not directly invaded the esophagus, trachea, or great vessels.

Summary of five cases

The clinical characteristics, treatment, and outcomes of the five cases presented are summarized in Table 1. Four patients

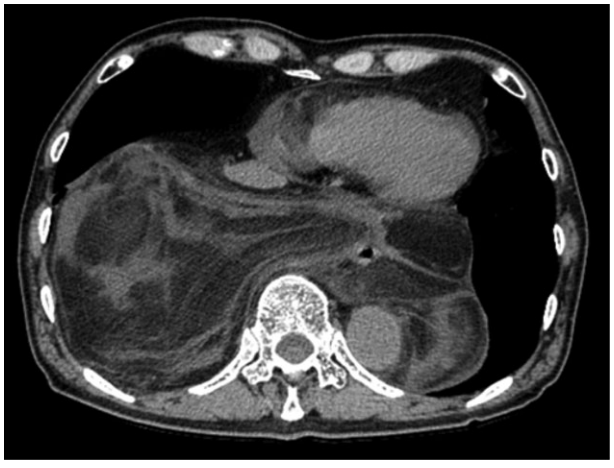

Figure 5 Preoperative computed tomography scan in Case 4. A huge tumor was detected in the posterior mediastinum, which projected on either side of the intrathoracic space. The esophagus was surrounded by the tumor.

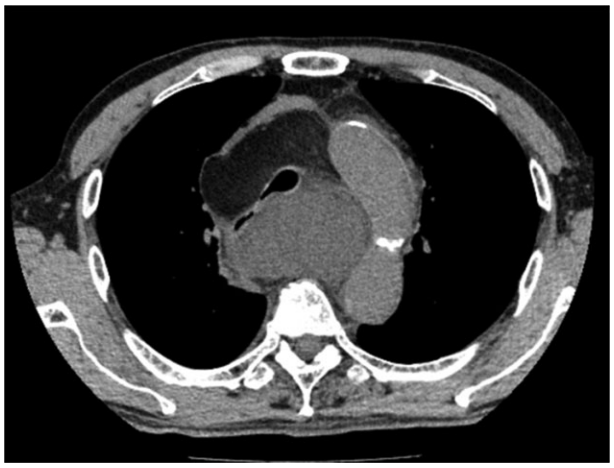

Figure 6 Chest computed tomography scan of Case 5 at the first visit. A giant tumor was observed in the middle and posterior mediastinum extensively surrounding the trachea.

Table 1 Summary of our five cases

Case	Age	Gender	Location	Symptom	Tumor size (cm)	SUVmax	Ki-67 (%)	FNCLCC grade	Initial treatment	Surgical approach	Recurrence	RFS (months)	Treatment for recurrence	OS	OS status
1	45	F	Middle	None	12.7	1.9	< 10	2	Surgery	Cervical approach, right sided VATS	Yes	51	Surgery	60	Alive
2	62	F	Superior	None	12	2.5	20	2	Surgery	Sternotomy	Yes	28	RT	48	Alive
3	84	M	Anterior	None	6.6	9.2	50	2	Surgery	Sternotomy	Yes	27	Surgery	40	Alive
4	75	M	Posterior	None	20	2.0	3	2	Surgery	Bilateral thoracotomy	No	3	—	3	Alive
5	78	M	Middle	Dyspnea, Hoarseness	11	5.1	40	2	Chemo (Doxorubicin)	—	—	—	—	0.5	Dead

Chemo, chemotherapy; FNCLCC, French Federation Nationale des Centres de Lutte Contre le Cancer; OS, overall survival; FRS, recurrence-free survival; RT, radiotherapy; SUVmax, maximum standardized uptake value; VATS, video-assisted thoracoscopic surgery.

were treated by surgical resection: cervical resection and right-side VATS (1 patient), bilateral thoracotomy with thoracoscopy (1 patient), and sternotomy (2 patients). Three of these four patients developed recurrence after surgical resection: two underwent repeat resection, while the remaining patient underwent heavy particle radiotherapy. Only one patient had chemotherapy as initial treatment using adriamycin. There was a weak positive association between SUVmax and Ki-67 positive ratio. All five cases were French Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grade 2.

Literature review

Nineteen cases of mediastinal dedifferentiated liposarcoma have been published in the English language literature, including our five cases (Table 2). The mean age of patients was 63.3 ± 13.2 and there was no difference in the gender ratio. The reports presented details of symptoms in 13 patients: seven complained of some symptoms, while the other six were asymptomatic and their tumors were discovered by chance. The most common symptom was dyspnea, followed by dysphagia and hoarseness. The tumor was located in the posterior mediastinum in more than half of the cases, followed by the anterior, middle, and superior mediastinum.

Discussion

We report five cases of mediastinal dedifferentiated liposarcoma and present some important clinical issues. First, three of four cases treated with radical surgical resection developed local recurrence within a few years after treatment, despite complete resection. However, repeat surgical resection or radiotherapy was effective for the local recurrence and the patients showed relatively long-term survival. In contrast, one patient received doxorubicin chemotherapy, which was not effective, and died within a month (Case 5). Therefore, we suggest that complete resection should be initially considered in cases of primary mediastinum dedifferentiated liposarcoma. In addition, repeat surgical resection should be considered in cases of local recurrence. Radiation therapy may be effective to control recurrent lesions.

There have been a number of case reports regarding mediastinal dedifferentiated liposarcoma;[1–3,6–9] however, few reports refer to long-term prognosis. Coulibaly *et al.* reported a case of recurrent dedifferentiated liposarcoma of the mediastinum involving the lung and pleura.[8] The patient showed recurrence 15 months after primary mediastinal tumor resection. Repeat surgical resection of the local recurrent tumor was incomplete, and the patient was administered adjuvant radiotherapy (60 Gy). Eight years

Table 2 Literature review of 19 cases published between 2002 and 2016, including our five cases

Authors	No. ofpatients	Age	Gender	Location	Symptom	Tumor size (cm)	Initial treatment	Surgical approach	Recurrence	RFS (months)	Treatment for recurrence	OS	OS status
Boland *et al*.[4]	5	68	M	Posterior	Unknown	Unknown	Surgery	Unknown	Yes	48	Unknown	72	Alive
		63	F	Anterior	Unknown	Unknown	Surgery	Unknown	Yes	24	Unknown	34	Dead
		47	F	Middle	Unknown	Unknown	Surgery	Unknown	No	60	Unknown	60	Alive
		71	F	Posterior	Unknown	Unknown	Surgery (incomplete)	Unknown	Residual	12	Unknown	12	Alive
		76	F	Anterior	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
Ortega *et al*.[5]	3	75	M	Posterior	Weight loss, dyspnea	14	Surgery	Unknown	Yes	Unknown	Unknown	6	Alive
		66	M	Posterior	Chest pain, dysphagia, malaise	9	Surgery	Unknown	No	Unknown	—	24	Alive
		53	F	Posterior	Dysphagia	23	Surgery	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
Chen *et al*.[6]	1	64	M	Unknown	Unknown	6	Surgery	Unknown	No	12	—	12	Alive
Fukai *et al*.[7]	1	56	M	Anterior	None	16.5	Surgery	Sternotomy	No	36	—	36	Alive
Hamanaka *et al*.[1]	1	74	M	Posterior	Dry cough	11	Surgery	Lateral thoracotomy	No	8	—	8	Alive
Coulibaly *et al*.[8]	1	34	F	Posterior	Dyspnoea	20	Surgery	Lateral thoracotomy	Yes	15	Surgery (incomplete)	114	Dead
Narasimman *et al*.[9]	1	48	M	Posterior	None	15	Surgery	Lateral thoracotomy	No	12	—	12	Alive
Hirai *et al*.[3]	1	64	M	Anterior	Hoarseness	6.5	Surgery	Sternotomy	No	14	—	14	Alive
Miura *et al*.	5	45	F	Middle	None	12.7	Surgery	Cervical approach, right sided VATS	Yes	51	Surgery	60	Alive
		62	F	Superior	None	12	Surgery	Sternotomy	Yes	28	RT	48	Alive
		84	M	Anterior	None	6.6	Surgery	Sternotomy	Yes	27	Surgery	40	Alive
		75	M	Posterior	None	20	Surgery	Bilateral thoracotomy	No	3	—	3	Alive
		78	M	Superior	Dyspnea, Hoarseness	11	Chemo (Doxorubicin)	—	—	—	—	0.5	Dead

Chemo, chemotherapy; OS, overall survival; FRS, recurrence-free survival; RT, radiotherapy; SUVmax, maximum standardized uptake value; VATS, video-assisted thoracoscopic surgery.

later, a second recurrence occurred in the pleura and lung, and the patient died after three months. Chen *et al.* studied 23 cases of primary intrathoracic liposarcoma, including lesions in the mediastinum, pleura, and lung.[6] They reported poor OS and RFS in the dedifferentiated type compared to the well-differentiated type, and two of four cases relapsed despite radical surgical resection. Chen *et al.* concluded that it is essential to ensure complete resection of the primary intrathoracic liposarcoma to cure the disease. However, the growth pattern of liposarcoma tends to be expansive rather than infiltrative. Patients often complain of few symptoms until the tumor grows very large, which may be one reason for incomplete resection. Four of our surgical patients, particularly Case 4, exhibited no symptoms despite having large tumors surrounding the trachea, esophagus, or great vessels.

The median RFS period of the three cases in our study was 35 months and all developed local recurrence in the mediastinum. Two patients underwent repeat surgical resection. However, one patient showed second local recurrence in the mediastinum and was treated with heavy particle radiotherapy. Another patient with recurrence received proton beam therapy, and was followed up for 17 months without a second recurrence. Only four cases of recurrence were found in the literature review, and showed recurrence a few years after the first surgical treatment.[4,5,8] Other reports did not refer to recurrence or the follow-up period was relatively short; therefore long-term prognosis after surgery is unclear. According to literature review, we speculate that there is no relationship between the tumor site and clinicopathological features, including prognosis.[1–9]

Based on the previous reports included in our review, complete surgical resection is the best method to cure mediastinal dedifferentiated liposarcoma.[1,3–9] En bloc resection should be attempted in such cases if possible. All of our surgical cases underwent en bloc resection without breaking the tumor capsule. Adhesion between the tumor and surrounding tissue was relatively weak, and there was no invasion to any surrounding organs. In addition, during autopsy of Case 5, direct invasion to the esophagus, trachea, or great vessels was not observed, suggesting that surgical resection should be considered as initial treatment. As much of the tumor and peripheral fat tissue should be removed as possible, although it is difficult to perform complete resection of fat tissue near the thyroid or thymus. In fact, atypical cells were found in the peripheral fat tissue in our four surgical cases. We consider adjuvant radiotherapy to be effective because radiotherapy to locally recurrent lesions was effective in this study, although its efficacy has not been established in dedifferentiated liposarcoma.

Chemotherapy is generally ineffective for liposarcoma. Jones *et al.* examined the differential sensitivity of liposarcoma subtypes to chemotherapy, and reported that myxoid liposarcoma was relatively chemosensitive compared to dedifferentiated or well-differentiated liposarcoma, and the response rate of dedifferentiated liposarcoma to first-line chemotherapy was only 25% (doxorubicin, 8%; doxorubicin plus ifosfamide, 17%).[10] The microtubule growth inhibitor, eribulin, has recently been approved for the treatment of advanced liposarcoma. Setola *et al.* reported that eribulin was highly effective in advanced liposarcoma.[11] The efficacy of chemotherapy against mediastinal liposarcoma has not been established. However, new developed agents should be evaluated in future clinical studies for use in the treatment of dedifferentiated liposarcoma. Dedifferentiated liposarcoma has genetic abnormalities with high-level amplifications of chromosome 12q14-15, including the MDM2 and CDK4 cell cycle oncogenes. Novel therapies targeted at the gene products of chromosome 12 are being tested in clinical trials.[12]

In 1984, the French Federation of Cancer Centers Sarcoma Group proposed the FNCLCC grading system, which reflects the malignancy of soft tissue tumors.[13] Our five cases were FNCLCC grade 2. Relationships between mediastinal dedifferentiated liposarcoma prognosis and the FNCLCC grading system remain unclear, thus further data is needed.

We evaluated Ki-67 immunostaining and SUVmax in five patients who underwent surgical treatment. SUVmax results were relatively low, but the two parameters showed a positive association and may be useful as prognostic factors. However, the number of cases reviewed in our study was small, thus long-term prognosis, clinicopathological features, and the optimal choice of treatment remain unclear. Further studies of larger patient samples would likely clarify the relationship between these biomarkers and the clinicopathological features of mediastinal dedifferentiated liposarcoma.

We would like to emphasize that aggressive treatment by surgical resection should initially be considered for mediastinal dedifferentiated liposarcoma. In addition, we suggest that repeat surgical resection or radiotherapy are appropriate treatment choices for locally relapsed mediastinal dedifferentiated liposarcoma.

Disclosure

No authors report any conflict of interest.

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