

Pleural dedifferentiated liposarcoma: A case report

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Received June 1, 2018; Accepted October 23, 2018

DOI: 10.3892/mco.2018.1757

Abstract. The present case report describes a rare case of pleural liposarcoma. A 45-year-old Japanese man was hospitalized for increasing left chest pain. Imaging revealed a 10-cm pleural tumor and a 1.7-cm contralateral right pulmonary nodule. Biopsy specimens of the pleural tumor showed undifferentiated spindle-shaped and/or rounded sarcomatous features with myxoid stroma. The patient underwent embolization of the arteries feeding the left pleural tumor and palliative partial resection of the pleural tumor. The surgically removed specimens exhibited similar undifferentiated sarcomatous features. The left pleural tumor regrew aggressively, and the patient succumbed to mortality ~4.2 months following hospitalization. Autopsy demonstrated a 35-cm left pleural tumor, metastasizing to both adrenal glands and lumbar vertebral bones, and a 2.2-cm primary adenocarcinoma of the right lung. The majority of the left pleural tumor and its metastases consisted of undifferentiated sarcomatous elements, however, scattered or aggregated lipoblasts were identified in localized areas adjacent to the diaphragm. Immunohistochemically, these lipoblasts were diffusely positive for MDM2 and focally positive for S-100 protein. Undifferentiated sarcomatous tumor cells were focally positive for MDM2 but negative for S-100 protein. This case was diagnosed as pleural dedifferentiated liposarcoma. The local aggressiveness of the pleural liposarcoma directly contributed to the patient's mortality. A review of the literature indicated that the dedifferentiated subtype may serve as a factor that is indicative of a poor prognosis for pleural liposarcoma.

Introduction

Liposarcoma is one of the most common types of sarcoma arising in adult soft tissues, accounting for 15-25% of all types of sarcoma (1-3), and is chiefly subclassified into four types; atypical lipomatous tumor and/or well-differentiated liposarcoma (ALT/WDL), dedifferentiated liposarcoma, myxoid liposarcoma, and pleomorphic liposarcoma (1,3). A diagnosis of liposarcoma requires histological evidence of lipoblastic differentiation, which may be easily recognizable in ALT/WDL, but is more difficult to assess in non-lipogenic sarcomatous regions within the dedifferentiated and pleomorphic subtypes. Liposarcoma usually arises in the extremities, retroperitoneum, mesenteric region, and shoulder area (1-3); its occurrence in the pleura is rare. To the best of our knowledge, only 30 cases of pleural liposarcoma have been previously reported in the English literature (4-21), and their clinicopathological features remain to be fully elucidated. The present case report discusses a recently encountered case of pleural dedifferentiated liposarcoma; the clinicopathological features of this case are described to expand on current knowledge of pleural liposarcoma.

Case report

A 45-year-old Japanese man was hospitalized in the Japan Self-Defense Forces Central Hospital (Tokyo, Japan) for rapidly increasing left chest pain. Computed tomography (CT) revealed a 10-cm left pleural tumor with hydrothorax and a 1.7-cm pulmonary nodule in the right upper lobe (Fig. 1A and B). ¹⁸F-fluorodeoxyglucose positron emission tomography (¹⁸F-FDG-PET) revealed FDG uptake in the left pleural tumor and the right pulmonary nodule, with maximum standardized uptake values in these lesions of 8.35-10.42 and 2.99-3.14, respectively. Hematological analysis and bronchoscopic examination revealed no significant findings. CT-guided percutaneous biopsy and thoracotomy-associated incisional biopsy of the left pleural tumor were performed. These specimens exhibited undifferentiated sarcomatous features. Embolization of the arteries feeding the left pleural tumor and palliative surgery were performed 1 month and 2.2 months later, respectively. Surgery consisted of partial resection of the pleural tumor and resection of the left lower and lingua lobes invaded by the tumor. Due to his worsened general condition, the patient was unable to receive additional chemotherapy.

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Abbreviations: ALT/WDL, atypical lipomatous tumor and/or well-differentiated liposarcoma; CT, computed tomography; ¹⁸F-FDG-PET, ¹⁸F-fluorodeoxyglucose positron emission tomography

Key words: liposarcoma, pleura, pleural cavity, dedifferentiated liposarcoma, autopsy, atypical lipomatous tumor, immunohistochemistry, MDM2

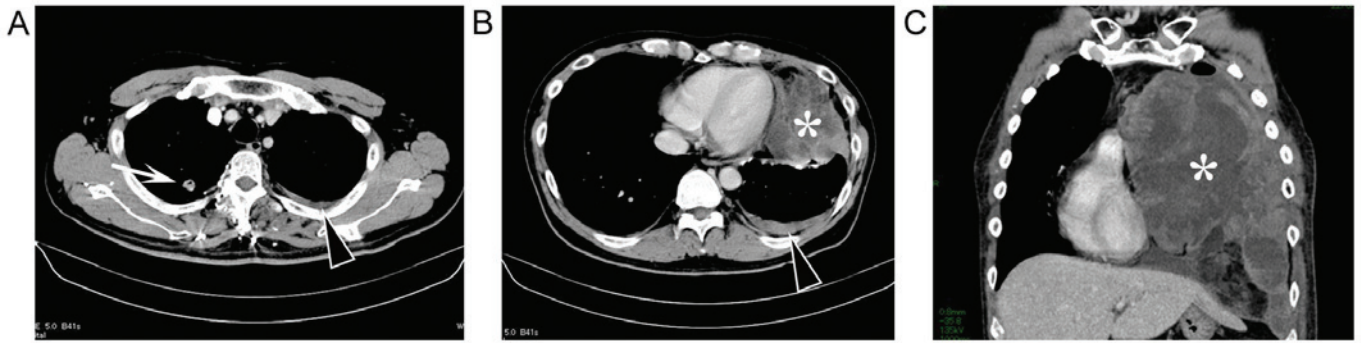


Figure 1. Computed tomography scan. The scan demonstrates a (A) right pulmonary nodule (arrow) and left pleural effusion (arrowhead), and a (B) left pleural tumor (asterisk) and left pleural effusion (arrowhead). (C) Following palliative surgery, a rapidly regrowing pleural tumor occupying the left pleural cavity was observed (asterisk).

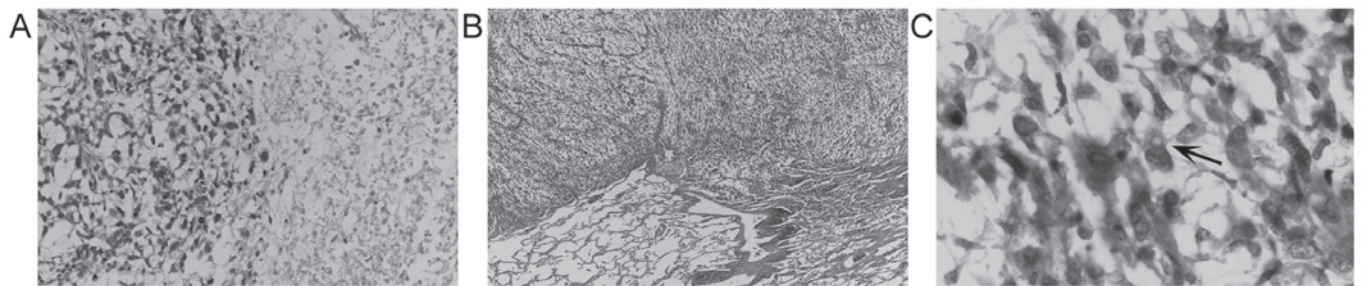


Figure 2. Hematoxylin and eosin histological staining of biopsy and surgical specimens of the left pleural tumor. (A) Percutaneous biopsy specimens show haphazard proliferation of undifferentiated tumor cells with necrosis (magnification, x200). (B) Surgically removed specimens show myxoid sarcomatous element invading the lung parenchyma (magnification, x40). (C) High-power view (magnification, x600) shows spindle-shaped and/or rounded tumor cells with swollen, irregular nuclei and an occasional intracytoplasmic vacuole (arrow).

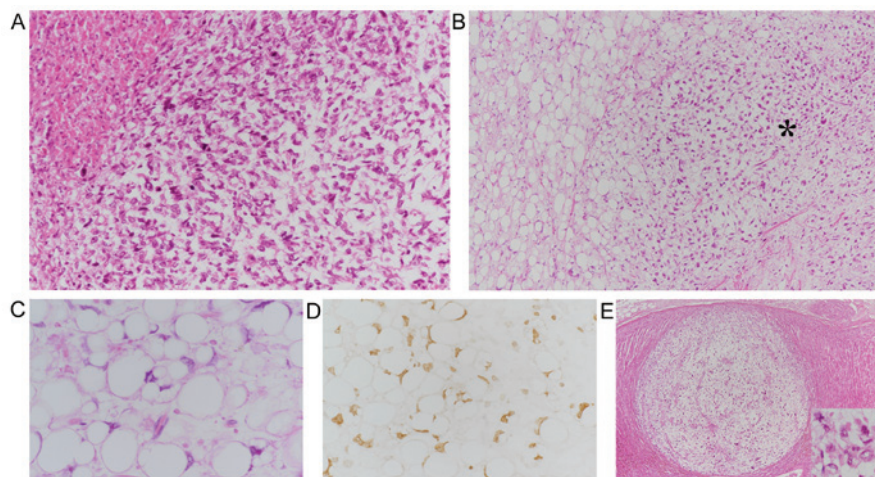


Figure 3. Autopsy findings of the left pleural tumor. (A) Majority of the tumor was composed of undifferentiated spindle-shaped and/or rounded undifferentiated cells (hematoxylin and eosin staining; magnification, x200). (B) Transition zone between undifferentiated tumor cells (asterisk) and lipogenic tumor cells, shown on the left (hematoxylin and eosin staining; magnification, x100). (C) High-power views of lipoblasts with centrally located irregular nuclei and a lipid-rich cytoplasm (hematoxylin and eosin staining; magnification, x600). (D) Immunohistochemical analysis of the expression of MDM2 shows nuclear positivity in lipoblasts (immunostaining; magnification, x400). (E) Hematoxylin and eosin staining shows myxoid sarcomatous elements metastasizing to the left adrenal gland (magnification, x40) and a high-power view (inset; magnification, x600).

The pleural tumor regrew rapidly following surgery and the mediastinum was shifted to the right (Fig. 1C). The patient's condition progressively deteriorated, and he succumbed to mortality from respiratory failure due to expansive growth of the pleural tumor ~4.2 months following hospitalization. Autopsy was performed.

The premortem biopsy specimens and surgically removed specimens were histologically composed of undifferentiated spindle-shaped and/or rounded cells with swollen irregular nuclei proliferating in a haphazard and/or fascicular manner with myxoid stroma and necrosis (Fig. 2). Only a few cells with a vacuolated cytoplasm were observed (Fig. 2C); however,

Table I. Clinicopathological features of 31 cases of pleural liposarcoma including the present case report.

Author (year)	Age (years)/sex	Site of pleura	Tumor size (cm)	Histology	Therapy	Follow-up/ months	Refs.
Ackerman and Wheeler (1942)	50/F	Left	NS	NS ^g	None (autopsy)	DOD/12	(4)
Gupta and Paolini (1967)	51/M	Right	21	Por	None (autopsy)	DOD/NS	(5)
D'Ambrosio (1974)	52/M	Left	NS	NS	C-Res	ANED/66	(6)
Wouters <i>et al</i> (1983)	19/M	Left	3.5	Myx	C-Res + Rad	Alive/55 ^h	(7)
Evans <i>et al</i> (1985)	45/M	Left	NS	Myx	None (autopsy)	DOO/0.07	(8)
McGregor <i>et al</i> (1987)	54/M	Right	2-25 ^a	WDL (>PL)	C-Res	DOU/108 ⁱ	(9)
Munk and Müller (1988)	27/F	Left	NS	NS	NS	NS	(10)
Carroll <i>et al</i> (1992)	23/F	Left	29, 21 ^b	Mixed	C-Res + Rad	ANED/16	(11)
Wong <i>et al</i> (1994)	38/M	Right	NS	My	C-Res + Rad	ANED/5	(12)
Okby and Travis (2000)	45/F	NS	16	Myx/Ro	P/I-Res + Chem	DOD/7	(13)
Okby and Travis (2000)	73/M	Right	NS	Myx	P/I-Res	DOD/9	(13)
Okby and Travis (2000)	67/M	Right	18.5	WDL	NS	DOU/16	(13)
Okby and Travis (2000)	80/M	Right	20	Myx	C- or P/I-Res	NS	(13)
Minniti <i>et al</i> (2005)	50/M	Left	13	WDL	C-Res + Rad	ANED/12	(14)
Takanami and Imamura (2005)	59/M	Right	12, 5.3 ^c	Dediff	C-Res	ANED/6	(15)
Goldsmith and Papagiannopoulos (2007)	42/M	Left	NS	Myx	C-Res + Rad	Alive/12 ^j	(16)
Goldsmith and Papagiannopoulos (2007)	80/F	Left	NS	Myx	P/I-Res	DOD/8	(16)
Benchetrit <i>et al</i> (2007)	76/F	Left	18, 11 ^d	Dediff	C- or P/I-Res	DOO/0.1	(17)
Peng <i>et al</i> (2007)	56/F	Left	NS	WDL	C-Res	ANED/18	(18)
Alloubi <i>et al</i> (2008)	58/M	Left	NS	Myx	C-Res + Rad	ANED/10	(19)
Chen <i>et al</i> (2014)	19/M	NS	NS	WDL	C-Res	Alive/56 ^k	(20)
Chen <i>et al</i> (2014)	30/F	NS	NS	WDL	C-Res	ANED/48	(20)
Chen <i>et al</i> (2014)	60/M	NS	NS	WDL	C-Res	ANED/43	(20)
Chen <i>et al</i> (2014)	20/F	NS	NS	Myx	C-Res	Alive/90 ^l	(20)
Chen <i>et al</i> (2014)	54/M	NS	NS	Myx	C-Res	ANED/26	(20)
Chen <i>et al</i> (2014)	41/M	NS	NS	Dediff	C-Res	Died/15 ^m	(20)
Chen <i>et al</i> (2014)	53/M	NS	NS	Dediff	C-Res	Died/11 ⁿ	(20)
Chen <i>et al</i> (2014)	61/M	NS	NS	WDL	P/I-Res	ANED/18	(20)
Chen <i>et al</i> (2014)	NA/F ^e	NA ^e	NA ^e	NA ^e	NA ^e	NA ^e	(20)
Wang <i>et al</i> (2017)	43/F	Left	21	Myx	C-Res	ANED/8	(21)
Present case (2018)	45/M	Left	10 ^f	Dediff	P/I-Res	DOD/4.2 ^o	-

^aPortions of four tumors were removed, including 25-, 22-, 2- and 2.5-cm tumors. ^bPortions of two tumors were removed, including 29- and 21-cm tumors. ^cPortions of two tumors were removed, including 12- and 5.3-cm tumors. ^dPortions of two tumors were removed, including an 18-cm tumor in the left pleural cavity and an 11-cm tumor in the posterior mediastinum. ^ePossibly due to a misprint in this article, the clinicopathological data of one female patient were not included. ^fTumor size initially detected by imaging. ^gFrom the illustration and the description in this article, the possibility of pleomorphic type exists. ^hA locally recurrent tumor was removed 55 months following initial surgery, and no evidence of disease was found thereafter. ⁱLocal recurrence was removed at 24 months post-surgery, and showed dedifferentiated features. ^jA recurrent tumor developed in an unreported site, for which the patient underwent additional surgery and chemotherapy 6 months following initial surgery. ^kA locally recurrent tumor developed 48 months following surgery, and was resected. ^lA locally recurrent tumor developed 47 months following surgery, and was resected. ^mA locally recurrent tumor developed 10 months following surgery, and was resected. ⁿA pulmonary metastasis was found 6 months following surgery, and was resected. ^oInterval following hospitalization. F, female; M, male; ANED, alive with no evidence of disease; Chem, chemotherapy; C-Res, complete resection; Dediff, dedifferentiated liposarcoma; DOD, died of disease; DOO, died of other disease; DOU, died of unknown cause; Myx, myxoid liposarcoma; Myx/Ro, myxoid and rounded type liposarcoma; NA, not available; NS, not stated; PL, pleomorphic liposarcoma; Por, poorly differentiated type; Rad, radiotherapy; P/I-Res, palliative and/or incomplete resection; WDL, well differentiated liposarcoma.

it was not possible to rule out non-specific vacuolar changes. Immunohistochemically, the tumor cells were positive for

vimentin only, and were negative for cytokeratin, S-100 protein, glial fibrillary acid protein, desmin, α -smooth muscle actin,

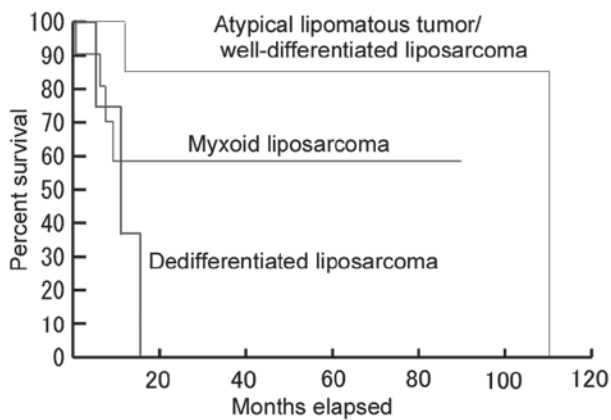


Figure 4. Kaplan-Meier survival curves of 23 patients with pleural liposarcoma for whom follow-up data were available. Log-rank tests demonstrated a significant difference in overall survival rate between patients with atypical lipomatous tumor/well-differentiated liposarcoma ($n=8$) and dedifferentiated liposarcoma ($n=4$; $P=0.001$), but failed to reveal significant differences between patients with myxoid liposarcoma ($n=11$), vs. atypical lipomatous tumor/well-differentiated liposarcoma ($P=0.141$) or between patients with myxoid, vs. dedifferentiated liposarcoma ($P=0.259$).

HMB-45, and myoglobin. Nuclear immunoreactivity for Ki-67 was observed in 26% of the tumor cells within the surgically removed specimens.

Postmortem examination revealed a 35-cm, whitish, necrotic solid tumor occupying the left thoracic cavity (Fig. 3A), which was directly invading the remnant left lung, chest wall, and diaphragm. Histologically, this pleural tumor exhibited predominantly myxoid sarcomatous features (Fig. 3A). However, in localized areas (~5% of the tumor volume) adjacent to the diaphragm, scattered or aggregated lipoblasts with occasionally scalloped swollen nuclei and lipid-rich cytoplasm were observed, some of which were intermingled with undifferentiated spindle-shaped or rounded tumor cells (Fig. 3B and C). The aggregated lipoblasts closely resembled those of lipoma-like ALT/WDL. These findings indicated a diagnosis of liposarcoma. The undifferentiated spindle-shaped/rounded tumor cells had metastasized to both adrenal glands (Fig. 3E) and the lumbar vertebral bones. By contrast, the 2.2-cm right pulmonary nodule was composed of columnar tumor cells proliferating in papillary, acinar, and focal lepidic patterns, indicating primary lung papillary-predominant adenocarcinoma. No metastases of pulmonary adenocarcinoma were observed. Immunohistochemically, the lipoblasts were diffusely positive for MDM2 (Fig. 3D) and focally and weakly positive for S-100 protein. The sarcomatous spindle-shaped/rounded cells were focally positive for MDM2, but were negative for S-100 protein. Autopsy also demonstrated severe pneumonia of the collapsed remnant left lung.

Discussion

In the present case study, the left pleural tumor had extensive involvement of non-lipogenic sarcomatous elements, with no lipoblastic features established on premortem examination. However, autopsy identified distinctive lipoblastic features intermingled with undifferentiated sarcomatous elements in the pleural tumor. The differential diagnoses included

dedifferentiated liposarcoma and pleomorphic liposarcoma. The former accounts for 18% of liposarcomas (1), characterized by the transformation from ALT/WDL and amplification of *MDM2* (1,3). The latter, pleomorphic liposarcoma, represents <15% of liposarcomas (1), which primarily develop *de novo* without ALT/WDL-like low-grade precursor lesions and without *MDM2* amplification (1,3,22-24). Previous studies (25,26) have reported that immunohistochemical evaluation of the expression of MDM2 provides suitable sensitivity for detecting *MDM2* gene amplification. In the present case study, autopsy identified ALT/WDL-like lesions within the primary tumor, and immunohistochemical evaluation revealed MDM2-positivity not only in the ALT/WDL-like lesions but also in sarcomatous spindle-shaped/rounded tumor cells. These findings suggest that the pleural tumor present was dedifferentiated liposarcoma.

Table I summarizes 31 cases of pleural liposarcoma, including 30 previously reported cases (4-21) and the present case study. Chen *et al* (20) described nine cases of pleural liposarcoma, however, tables in this article listed 10 cases of 'pleural' liposarcoma. Therefore, the clinicopathological features of one female case are unclear. The patients included 20 men and 11 women. For the 30 patients whose ages were known, the age ranged between 19 and 80 years (mean, 49.6 years). A total of 14 tumors involved the left pleural cavity, six arose in the right pleural cavity, and the sites of the other 11 tumors were unknown. In the 26 tumors for which the histological subtype was reported, myxoid or myxoid/rounded liposarcoma accounted for 12 (46%), which is higher than the proportion of myxoid liposarcomas within all types of liposarcoma. Other subtypes included eight ALT/WDLs (31%), five dedifferentiated liposarcomas (19%), and one mixed type (4%). The proportion of the dedifferentiated type liposarcomas is similar to that reported for all liposarcomas.

Among the 23 patients for whom follow-up data and the histological type of the liposarcoma were available, six of eight (75%) patients with pleural ALT/WDL were alive during months 12-56 of follow-up, whereas only one of the four (25%) patients with pleural dedifferentiated liposarcoma remained alive without disease during the 6 months of follow-up (Fig. 4). A log-rank test demonstrated a significant difference in overall survival rate between patients with ALT/WDL and dedifferentiated liposarcoma ($P=0.001$). Therefore, dedifferentiated histology appears to be a negative prognostic factor for pleural liposarcoma. No statistically significant differences were observed between patients with ALT/WDL, vs. myxoid liposarcoma ($P=0.141$) or between patients with myxoid, vs. dedifferentiated liposarcoma ($P=0.259$). In the 18 reported cases of completely resected pleural liposarcoma for which follow-up data were available, 15 (83%) patients were alive during months 6-90 of follow-up, with or without recurrence. These findings provide support for the previously reported concept that radical surgery may be a positive prognostic factor for liposarcoma (3,20), although the remaining three (17%) patients succumbed to mortality during months 11-108 of follow-up (9,20). Recurrent growth following complete resection was observed in seven (39%) of these patients (7,9,16,20), including five cases of local recurrence, one of pulmonary metastasis, and one recurrence at an unreported location. The case of pulmonary metastasis developed in a patient with dedifferentiated liposarcoma (20). In the present case report, the initially detected pulmonary nodule was primary lung adenocarcinoma, and not a metastasis, which may have

been responsible for the differences in maximum standardized uptake values between these lesions in the premortem FDG-PET examination. In addition, in the present case report, adrenal and bone metastases of liposarcoma were observed. However, the reason for the patient succumbing to mortality was considered to be due to the local aggressiveness of pleural liposarcoma, rather than to those metastases.

In conclusion, the present case report describes a case of pleural liposarcoma diagnosed upon autopsy. Premortem examination revealed myxoid sarcomatous features only, whereas autopsy identified scattered or aggregated MDM-positive lipoblasts, suggesting dedifferentiated liposarcoma. The local aggressiveness of this tumor directly contributed to the patient's clinical course.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

All data generated or analyzed during the present study are included in this published article.

Authors' contributions

SM, YU, YK, and HT analyzed the histopathological features. YO, KO, and TT provided clinical data, and re-analyzed them. YU collected previously reported articles. SM drafted the manuscript, and the remaining authors (YO, YU, KO, TT, YK, and HT) commented on the manuscript. SM and HT revised the manuscript.

Ethics approval and consent to participate

This retrospective study was performed according to the Declaration of Helsinki. Although the patient succumbed to mortality, the patient's father provided written informed consent for autopsy examination and related further investigation.

Patient consent for publication

The patient's father provided written informed consent for publication of the study.

Competing interests

The authors declare that they have no competing interests.

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