Pulmonary Metastasis From Liposarcoma

A Clinicopathologic and Immunohistochemical Study of 24 Cases

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Abstract

A review of the histologic features of pulmonary metastasis and clinical implications of liposarcoma (LS) is given for 24 cases (8 each) of the 3 types of LS: myxoid LS (ML), pleomorphic LS (PL), and dedifferentiated LS (DDL). Most patients were men. Metastatic ML and PL were distributed almost equally among the lung lobes, whereas DDL was more common in the left lower lobe. The metastatic MLs had variable cellularity ranging from singly scattered cells in a hyalinized stroma (treatment-related effect) to hypercellular ML. Most PLs (6/8) were nonlipogenic and resembled an undifferentiated pleomorphic sarcoma. All metastatic DDLs had high-grade histologic features and were predictably nonlipogenic. After pulmonary metastasectomy, 2 patients with ML and 1 with PL were disease-free. The other 6 patients with ML, 7 with PL, and all with DDL had progressive disease. The morphologic features of LS metastatic to the lungs seem diverse but within the spectrum of the histologic type expected from the primary tumor. Overall, the general trend for these LS subsets is progressive disease, metastatic disease for ML and PL with a much shorter interval for PL, and metastatic disease and local recurrence for DDL.

Most soft tissue tumors metastasize to the pulmonary bed during their clinical evolution,[1] although liposarcomas are reported to have a tendency to spread to extrapulmonary sites.[2] Studies have shown that this predilection to extrapulmonary metastasis is true for myxoid liposarcoma (ML) only,[3-5] not for pleomorphic liposarcoma (PL)[4,6] and dedifferentiated liposarcoma (DDL).[4,7] The other type of liposarcoma, atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDL), is not expected to metastasize unless dedifferentiation occurs.[4,7,8]

Like other tumors,[9] the metastatic foci of liposarcoma might differ in histologic features from the primary tumor and often are more cellular with fewer lipoblasts or even nonlipogenic.[4] We have encountered a few cases in which the pulmonary metastasis did not resemble the primary tumor. During the early phase of the specimen workup, the information about resection of primary adipose tumor was not disclosed; therefore, the list of entities considered was necessarily long. There seems to be a significant difference in prognosis between liposarcoma with lung metastasis and nonlipogenic sarcomas with lung metastasis.[10] The latter group has more aggressive behavior, demanding an accurate histopathologic diagnosis.

The present study was undertaken to describe the histologic spectrum of pulmonary metastasis from liposarcomas and the clinical implications of the different histomorphologic features of these metastatic foci.

Materials and Methods

All cases diagnosed as liposarcoma with pulmonary metastasis seen at the departments of pathology at the University of

Texas M.D. Anderson Cancer Center, Houston, and Ohio State University, Columbus, from January 1988 to December 2003 were retrieved. All available materials, including H&E-stained sections, conventional stains, and immunohistochemical stains, were reviewed. If original materials were not in the file, recuts from stored paraffin blocks were examined for primary and metastatic tumors. Clinical information was obtained from medical records and contributing physicians.

The histologic type of liposarcoma, site of primary tumor, sites of metastasis, interval between diagnosis of primary tumor and appearance of metastasis, treatment, length of follow-up (from date of first histopathologic diagnosis), and status at last follow-up were recorded. Most of the terms used in the present study are defined based on the 2002 World Health Organization classification of tumors of soft tissue and bone.[11] *ALT/WDL* is a locally infiltrative lipogenic tumor composed of mature fat and scattered atypical stromal cells. *DDL* is a nonlipogenic tumor arising from ALT/WDL de novo or as a recurrence from a previously resected ALT/WDL; dedifferentiation is recognized as low grade when lesional cells are spindle-shaped and with minimal atypia and high grade when there is considerable atypia resembling fibrosarcoma or an undifferentiated pleomorphic sarcoma.[3] *Round cell liposarcoma* (RCL) is used synonymously with *cellular ML* and considered a variant of ML. An area of ML is deemed to represent RCL/cellular ML when it is hypercellular and the cells are closely apposed with minimal or no intervening space between cells and the characteristic vascular pattern is inconspicuous.[3] *PL* is a mesenchymal neoplasm with lipoblasts and other lesional cells with atypia approximating that of malignant fibrous histiocytosis (MFH) or its variants.[3]

Results

Thirty cases of liposarcoma during this period had resection of 1 or more metastatic tumors to the lungs. Of the 30 cases, 6 were excluded owing to inadequate clinical history. A total of 24 cases representing 8 cases each of ML, PL, and DDL formed the study population.

Myxoid Liposarcoma

Clinicopathologic Features

The patients were predominantly men (M/F ratio, 7:1) **Table 1**. The patients' ages ranged from 31 to 61 years (mean, 45.9 years). The primary sites were gluteal and groin areas (4) and lower extremity (4). All primary tumors were resected. The status of the margin of resection and additional treatments are summarized in Table 1.

Metastatic Tumors to the Lungs

The lungs were the initial site of metastasis in 6 cases and the only metastatic site in 3 **Table 2**. The initial lung metastases were solitary in 3 cases **Image 1** and 3 or more in 5 cases.

Initial metastatic tumor was seen in all lobes of the lung, except right middle lobe. The left lower lobe was involved in 3 cases and the right upper lobe, right lower lobe, and left upper lobe at least once. Three cases had both lungs involved by tumor, but the lobe was not specified (Table 2). The number of nodules resected ranged from 1 to 7 per patient.

In 4 cases, typical ML histologic features were observed as small foci in a tumor or representing the entire tumor. Cellular ML (RCL) was the sole or predominant type in 2 cases and was seen as small foci in 1 case. In 3 patients who received neoadjuvant chemotherapy, extensively hyalinized and hypocellular tumor, changes considered treatment-related, were seen in 2 patients; the third patient had minimal treatment effect (case 3) **Table 3**.

In all metastatic nodules, the component tumor cells were relatively uniform without considerable variation in size and shape of cells. Lipoblasts were seen in 3 cases and were of the signet-ring type (Table 3) **Image 2** and **Image 3**.

The outline of each metastatic nodule appeared well circumscribed. The central portion of the nodules often was the least cellular area, and, frequently, the viable-looking tumor cells were concentrated at the periphery of the nodules. At the periphery of the nodules, both tumor cells and hyalinized parts of the nodule expanded the lung interstitium, often appearing as bulbous papillae protruding into the alveolar spaces covered by hyperplastic alveolar epithelium. Singly

Table 1
Myxoid Liposarcoma: Location and Treatment of Primary Tumor

Case No./Sex/Age (y)	Location	Treatment	Margin of Resection
1/M/31	Gluteal area, thigh	Preoperative radiation, resection	Negative
2/M/46	Gluteal area, flank	Preoperative chemotherapy, radiation, resection	Negative
3/M/48	Groin, thigh	Preoperative chemotherapy, radiation, resection	Unknown
4/M/43	Foot (heel)	Resection, postoperative radiation	Negative
5/M/61	Buttock	Preoperative chemotherapy, resection	Positive
6/M/47	Lower leg (calf)	Preoperative chemotherapy, radiation, resection	Negative
7/F/60	Thigh	Resection, postoperative chemotherapy, radiation	Unknown
8/M/31	Thigh	Resection, postoperative radiation; chemotherapy for local recurrence	Positive

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scattered or clusters of infiltrating tumor cells were observed rarely. Lymphovascular invasion was not identified.

In 1 case of nonlipogenic cellular ML (case 6), the component cells were arranged in a vague nesting pattern with round cells and discrete hyalinization resembling melanoma and/or a neuroendocrine neoplasm. In addition, owing to the partly myxoid stroma, epithelioid hemangioendothelioma also was considered as a diagnosis. These entities were ruled out owing to nonreactivity of tumor cells to antibodies against cytokeratin, S-100 protein, CD34, and CD31 by immunohistochemical analysis.

Clinical Course

The follow-up period ranged from 31 to 168 months (mean, 71.6 months) (Table 2). Two patients (cases 3 and 6) had no evidence of disease after resection of lung metastasis at 58 and 102 months of follow-up. One patient (case 4) died of disease 92 months after diagnosis of primary tumor, 4 patients had progressive disease at 36 to 168 months of follow-up, and 1 patient (case 1) had stable disease assessed after 42 months of follow-up.

Pleomorphic Liposarcoma

Clinicopathologic Features

All 8 cases of PL involved male patients **Table 4**. Their ages ranged from 14 to 58 years (mean, 42.8 years). The primary sites involved different anatomic areas. All primary tumors were resected. The status of margin of resection and additional treatments are summarized in Table 4.

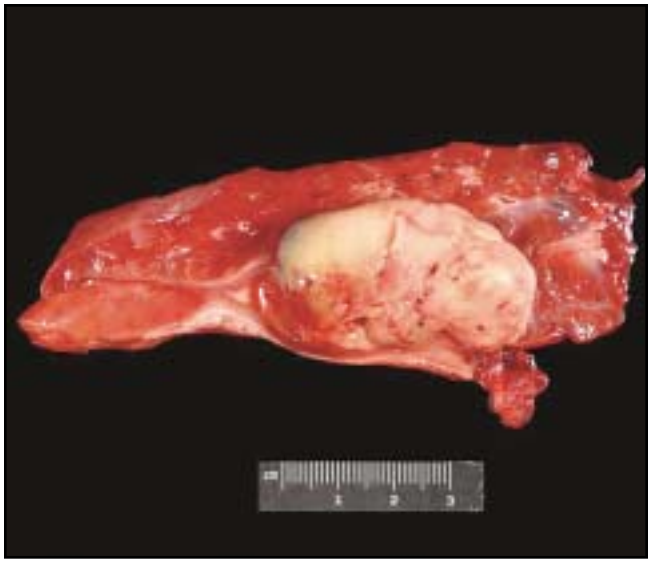

Image 1 Liposarcoma metastatic to lung parenchyma.

Metastatic Tumors to the Lungs

The lungs were the initial site of metastasis in 7 of 8 patients **Table 5**. There was 1 metastatic focus in 2 patients, 2 metastatic foci in 2, and multiple metastatic foci in 4. All

Table 2
Myxoid Liposarcoma: Pulmonary and Extrapulmonary Metastasis and Follow-up

	Lung Metastasis				Extrapulmonary Metastasis			
Case No./ Sex/Age (y)	Lung Lobe*	No. of Nodules	Time Interval (mo)	Treatment	Site	Time Interval (mo)	Treatment	Status at Last Follow-up (mo)
1/M/31	1, RLL, LUL	3	5	Preoperative chemotherapy, resection	Mediastinum	37	Chemotherapy	Progressive disease (42)
	2, RLL, RML	3	37	Preoperative chemotherapy, resection	—	—	—	—
2/M/46	1, Bilateral lungs	Multiple	18	Resection	None	—	—	Progressive disease (44)
	2, Bilateral lungs	Multiple	26	Chemotherapy	—	—	—	—
3/M/48	RUL	1	48	Resection	None	—	—	No evidence of disease (58)
4/M/43	Bilateral lungs	Multiple	87	Preoperative chemotherapy, resection	Axilla, bone, retroperitoneum, jejunum	86	Preoperative chemotherapy and resection	Died of disease (92)
5/M/61	LLL	1	144	Resection	Chest wall, mediastinum	158-163	Resection and palliation	Progressive disease (168)
6/M/47	LLL	1	82	Resection	None	—	—	No evidence of disease (102)
7/F/60	1, Bilateral lungs	Multiple	15	Postoperative chemotherapy, resection	Chest wall, abdomen, liver, pelvis	12-27	Preoperative chemotherapy, resection, and palliation	Progressive disease (31)
	2, Unspecified lobe	1	27	Postoperative - chemotherapy, resection	—	—	—	—
8/M/31	LLL	Multiple	24	Resection, postoperative chemotherapy	Mesentery, paraspinal and parasellar regions	31	Chemotherapy	Progressive disease (36)

LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.
* Numbers refer to episode of metastasis.

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Table 3
Myxoid Liposarcoma: Histopathologic Features of Primary Tumor and Lung Metastasis

Case No.	Primary Tumor	Lung Metastasis	Treatment Before Resection
1	Cellular	First, hyalinized and paucicellular tumor; second, typical ML and cellular ML, lipogenic	Chemotherapy
2	Typical	Typical ML	None
3	Cellular	Typical ML, lipogenic	Chemotherapy
4	Cellular	Predominantly hyalinized and paucicellular tumor	Chemotherapy
5	Cellular	Cellular ML, small foci of typical ML	None
6	Typical	Cellular ML*	None
7	Typical	Typical ML, lipogenic	None
8	Typical	Typical ML	None

ML, myxoid liposarcoma.
* Negative for cytokeratin, CD31, CD34, and S-100.

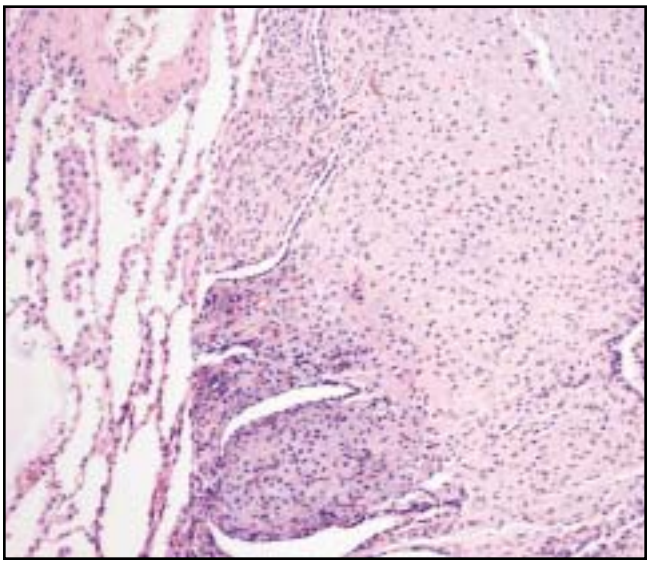

Image 2 Myxoid liposarcoma metastatic to the lung (H&E, ×30).

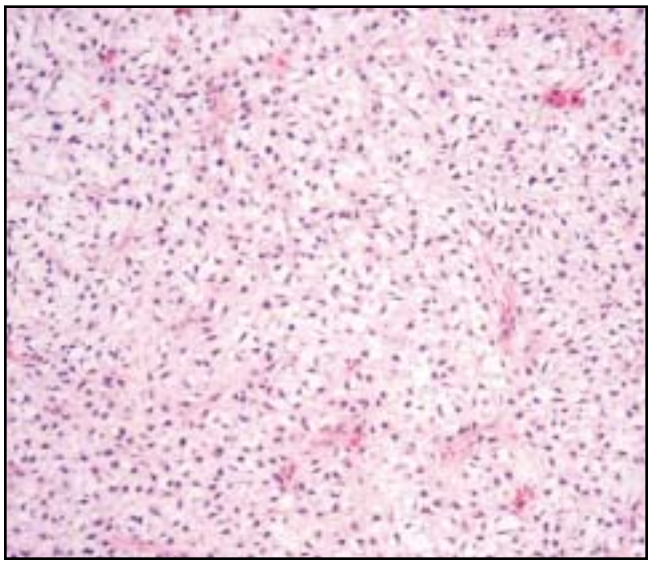

Image 3 High-power view of a myxoid liposarcoma metastatic to the lung (H&E, ×30).

lung lobes had 2 metastatic foci each; 1 had bilateral lung metastasis (involved lung lobes were not specified).

Of 8 cases, 6 were nonlipogenic. All metastatic nodules consisted predominantly of medium to large lesional cells with variable numbers of pleomorphic cells, including bizarre and giant cells. Mitoses were numerous. Three cases had tumor necrosis. Considerable myxoid background was present in 3 cases. Of the 2 lipogenic tumors, 1 (case 4) had numerous signet-ring lipoblasts with scattered pleomorphic forms **Image 4** and **Image 5**. Of the 4 postchemotherapy cases, 2 had extensive stromal hyalinization. Often, the periphery of the nodules was made irregular by invading tumor, dispersed in single cells or in tight clusters. Hyperplastic alveolar epithelium as seen in ML was seen

Table 4
Pleomorphic Liposarcoma: Location and Treatment of Primary Tumor

Case No./Sex/Age (y)	Location	Treatment	Margin of Resection
1/M/52	Shoulder	Preoperative chemotherapy, resection	Negative
2/M/52	Breast	Resection, postoperative chemotherapy	Unknown
3/M/48	Lower leg (tibia)	Resection, postoperative radiation	Negative
4/M/18	Thigh	Preoperative chemotherapy, radiation, resection	Unknown
5/M/52	Arm	Resection	Positive
6/M/58	Parietal pleura	Resection, chemotherapy	Unknown
7/M/48	Retroperitoneum	Resection, postoperative radiation	Unknown
8/M/14	Mediastinum	Resection, postoperative chemotherapy for local recurrence	Unknown

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Table 5
Pleomorphic Liposarcoma: Pulmonary and Extrapulmonary Metastasis and Follow-up

	Lung Metastasis				Extrapulmonary Metastasis			
Case No./ Sex/Age (y)	Lung Lobe*	No. of Nodules	Time Interval (mo)	Treatment	Site	Time Interval (mo)	Treatment	Status at Last Follow-up (mo)
1/M/52	1, LUL	1	0	Postoperative chemotherapy, resection	Mediastinum, abdomen, peripancreatic region	18	Unknown	Progressive disease (18)
	2, RUL, RML	Multiple	18	—	—	—	—	—
2/M/52	1, RUL	Multiple	107	Preoperative chemotherapy, resection	Perineum, scalp, neck, upper arm, chest, mediastinum, thoracic spine, abdomen	130	Resection and chemotherapy	Progressive disease (130)
	2, Left lung	Multiple	119	Preoperative chemotherapy, resection	—	—	—	—
	3, Bilateral	Multiple	130	—	—	—	—	—
3/M/48	1, LLL, RML	Multiple	14	Resection	Mediastinum	25	Unknown	Progressive disease (25)
	2, Bilateral	Multiple	20	Chemotherapy	—	—	—	—
	3, Bilateral	Multiple	25	—	—	—	—	—
4/M/18	1, RML	1	14	Resection	Paravertebral soft tissue, chest wall, thoracic spine	10-11	Resection and palliation	Progressive disease (131)
	2, Bilateral	Multiple	131	Resection	—	—	—	—
5/M/52	LUL, LLL	2	6	Preoperative and postoperative chemotherapy, resection	None	—	—	No evidence of disease (42)
6/M/58	RUL, RLL	Multiple	12	Resection, postoperative chemotherapy	None	—	—	Stable disease (15)
7/M/48	1, RLL	2	29	Resection	Thoracic vertebra, paraspinal soft tissue, left ventricle (heart)	30-72	Resection, radiation, chemotherapy, palliation	Progressive disease (72)
	2, LLL	1	30	Chemotherapy, resection	—	—	—	—
	3, Right lung	Multiple	32	Resection	—	—	—	—
	4, LLL	Multiple	43	Chemotherapy	—	—	—	—
8/M/14	Bilateral	Multiple	3	Resection, postoperative chemotherapy	None	—	—	Progressive disease (15)

LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.
* Numbers refer to episode of metastasis.

infrequently. Vascular invasion was identified in 1 tumor (case 1) **Table 6**.

Metastatic melanoma was considered and ruled out in 2 tumors (cases 6 and 7). Both tumors were negative for S-100 protein and HMB-45; case 7 also was negative for MART-1.

Clinical Course

One patient (case 5) had no evidence of disease after 42 months of follow-up (36 months after resection of 2 lung metastases) (Table 5). Another patient (case 6) had stable disease assessed 3 months after resection of lung metastasis and 15 months after resection of the primary tumor; this patient had multiple metastases involving only the lungs. The other 6 patients had multiple metastases with progressive disease at last follow-up. In 5 of these 6 patients, multiple pulmonary and extrapulmonary metastases developed subsequently after the initial pulmonary metastasis. One patient (case 8) had local recurrence (mediastinum) 3 months after excision of the primary tumor.

Dedifferentiated Liposarcoma

Clinicopathologic Features

The patients were predominantly men (M/F ratio,7:1). Their ages ranged from 37 to 77 years (mean, 58.4 years). Primary sites were distributed as follows: retroperitoneum, 4; mediastinum, 2; and scrotum or spermatic cord, 2. All primary tumors were resected. The status of margin of resection and additional treatments are summarized in **Table 7**.

De novo DDL was present in 5 cases. Three patients (cases 1, 2, and 6) had an original diagnosis of ALT/WDL at the primary site, and a diagnosis of DDL was established based on the histologic features of the lung metastasis. All 3 patients had local recurrence. One patient (case 6) had recurrence of "hernia" at the scrotal area with eventual histologic findings of a dedifferentiated component on the third resection, 34 months after the first "herniorrhaphy" **Table 8**.

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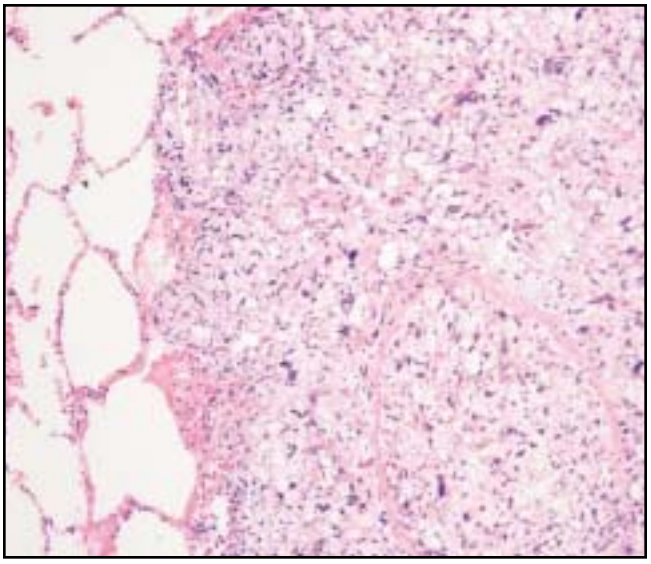

Image 4 Low-power view of a pleomorphic liposarcoma metastatic to the lung (H&E, ×30).

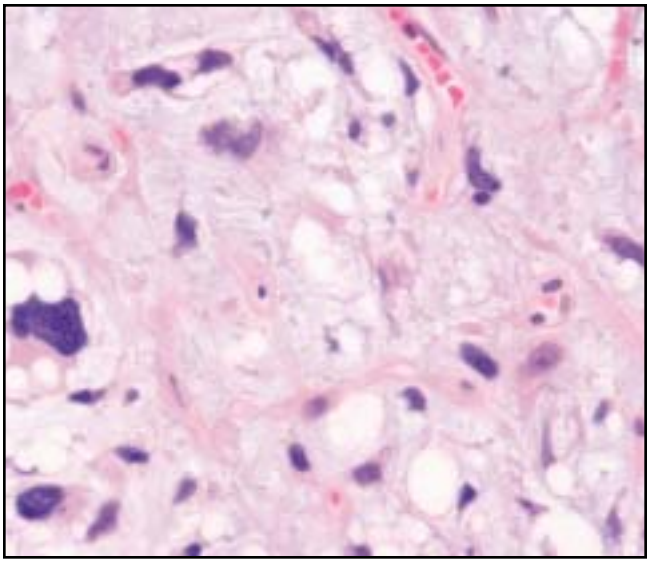

Image 5 High-power view of a pleomorphic liposarcoma metastatic to the lung (H&E, ×40).

Metastatic Tumors to the Lungs

The lungs were the initial site of metastasis in all cases and the only site of metastasis in 3 cases (Table 8). The initial lung metastases ranged from single to multiple foci. One metastatic focus was seen in 6 patients, and multiple foci were seen in 2 patients. All metastases involved the left lung: left upper lobe, 2; left lower lobe, 4; "left lung," 1; and bilateral, 1. The maximum number of metastatic nodules resected from a patient was 5.

All 8 metastatic nodules were nonlipogenic **Table 9**. The histomorphologic features in 3 patients (cases 6, 7, and 8) were those of MFH composed of pleomorphic cells with admixed bizarre giant cells and multinucleated cells **Image 6**. Rhabdomyosarcomatous differentiation was present in 1 (case 6). Of the 5 nodules resected from case 7, 4 were cellular and 1 was hypocellular and extensively hyalinized. The tumor of the third patient (case 8) had no specific mesenchymal histologic features and was consistent with undifferentiated high-grade pleomorphic sarcoma.[12] Of these 3 patients, 2 received preresection chemotherapy, including the patient (case 8) with a hyalinized and partly necrotic tumor nodule.

One patient (case 1) had features of fibroblastic osteosarcoma consisting of spindle cells in fascicles alternating with well-formed bone matrix lined by osteoblasts. Two other patients (cases 2 and 4) had spindle cell sarcoma; both tumors had interlacing short fascicles of noticeably atypical spindle cells with a subtle storiform pattern.

The outline of the metastatic nodules was jagged as a result of tumor cells infiltrating into the lung parenchyma, a feature similar to those seen in metastatic nodules of PL. Tumor infiltration was less conspicuous in the spindle cell sarcomatous nodules, including that of the fibroblastic osteosarcoma

Table 6
Pleomorphic Liposarcoma: Histopathology of Primary Tumor and Lung Metastasis

Case No.	Primary Tumor	Lung Metastasis*	Treatment Before Resection
1	PL	1, Pleomorphic sarcoma: necrosis, myxoid background, nonlipogenic, infiltrative edges	None
		2, Pleomorphic sarcoma: necrosis, myxoid background, nonlipogenic, infiltrative edges	None
2	PL	Pleomorphic sarcoma with extensive fibrosis: nonlipogenic	None
3	PL	Pleomorphic sarcoma: nonlipogenic	None
4	PL	Pleomorphic sarcoma: myxoid background, lipogenic, infiltrative edges	Chemotherapy
5	PL	Pleomorphic sarcoma: singly scattered large cells in a hyalinized stroma, nonlipogenic	Chemotherapy
6	ALT/WDL and PL	Pleomorphic sarcoma: tumor necrosis, myxoid background, nonlipogenic	Chemotherapy
7	PL	Pleomorphic sarcoma: collagenous stroma, nonlipogenic	Chemotherapy
8	PL	Pleomorphic sarcoma: necrosis, nonlipogenic	Chemotherapy

ALT, atypical lipomatous tumor; PL, pleomorphic liposarcoma; WDL, well-differentiated liposarcoma.
* Numbers refer to episodes of metastasis.

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Table 7
Dedifferentiated Liposarcoma: Location and Treatment of Primary Tumor

Case No./Sex/ Age (y)	Location	Treatment	Margin of Resection
1/M/55	Anterior mediastinum	Preoperative chemotherapy, resection; chemotherapy for local recurrence	Unknown
2/F/77	Retroperitoneum	Resection; unspecified for local recurrence	Unknown
3/M/37	Retroperitoneum	Resection for primary tumor; resections for 4 local recurrences	Unknown
4/M/68	Mediastinum	Resection, postoperative chemotherapy; resection for first recurrence; unknown for second recurrence	Unknown
5/M/45	Retroperitoneum	Resection, postoperative chemotherapy; chemotherapy for local recurrence	Positive
6/M/71	Scrotum	Resection (orchiectomy), postoperative radiation; resection and postoperative radiation for first and second local recurrences	Unknown
7/M/63	Spermatic cord	Resection (orchiectomy), postoperative radiation, postoperative chemotherapy	Positive
8/M/51	Retroperitoneum	Resection, postoperative radiation; resection for first local recurrence; not available for second local recurrence	Unknown

Table 8
Dedifferentiated Liposarcoma: Pulmonary and Extrapulmonary Metastasis and Follow-up

	Lung Metastasis				Extrapulmonary Metastasis			
Case No./ Sex/Age (y)	Lung Lobe*	No. of Nodules	Time Interval (mo)	Treatment	Site	Time Interval (mo)	Treatment	Status at Last Follow-up (mo)
1/M/55	Left lung	1	30	Resection (left-sided pneumonectomy)	None	—	—	Progressive disease (33)
2/F/77	1, Bilateral	Multiple	12	Resection	Psoas muscle and liver	24	Unknown	Progressive disease (29)
	2, Bilateral	Multiple	24	—	—	—	—	—
3/M/37	1, LUL	1	216	Resections and chemotherapy	Kidney, small intestine large intestine, abdominal wall, shoulder, thigh	216-277	Resection and postoperative chemotherapy	Progressive disease (288)
	2, RUL	Multiple	252	Resection and chemotherapy	—	—	—	—
	3, Right lung	Multiple	264	Resection and chemotherapy	—	—	—	—
	4, Bilateral	Multiple	277	Chemotherapy	—	—	—	—
4/M/68	1, LLL	2	38	Resection	Diaphragm, buttock, chest wall, mediastinum	38-63	Resection and palliation	Progressive disease (63)
	2, LLL	Multiple	63	—	—	—	—	—
5/M/45	1, LLL	1	0	Resection and post-operative chemotherapy	None	—	—	Progressive disease (10)
	2, Bilateral	Multiple	10	—	—	—	—	—
6/M/71	1 (lingual and LLL)	1	34	Resection	Mediastinum, pleura	34	Resection	Progressive disease (34)
7/M/63	1, LUL, LLL	Multiple	9	Preoperative chemotherapy and resection	None	—	—	Progressive disease (18)
	2, Bilateral	Multiple	18	—	—	—	—	—
8/M/51	LLL	1	105	Preoperative chemotherapy and resection	Neck, abdomen, pelvis, scrotum	50-105	Resection	Progressive disease (123)

LLL, left lower lobe; LUL, left upper lobe; RUL, right upper lobe.
* Numbers refer to episodes of metastasis.

Table 9
Dedifferentiated Liposarcoma: Histopathologic Features of Primary Tumor and Lung Metastasis

Case No.	Primary Tumor	Lung Metastasis	Treatment Before Resection
1	ALT/WDL	Fibroblastic osteosarcoma, nonlipogenic	None
2	ALT/WDL	Spindle cell sarcoma, nonlipogenic	None
3	ALT/WDL and DDL	Pleomorphic sarcoma, nonlipogenic	None
4	ALT/WDL and DDL	Spindle cell sarcoma, nonlipogenic	None
5	ALT/WDL and DDL	High-grade osteosarcoma	Chemotherapy
6	ALT/WDL	Pleomorphic sarcoma with rhabdomyosarcoma	None
7	ALT/WDL and DDL	Pleomorphic sarcoma, myxoid background; 1 of 5 nodules was hyalinized	Chemotherapy
8	ALT/WDL and DDL	High-grade pleomorphic sarcoma	Chemotherapy

ALT, atypical lipomatous tumor; DDL, dedifferentiated liposarcoma; WDL, well-differentiated liposarcoma.

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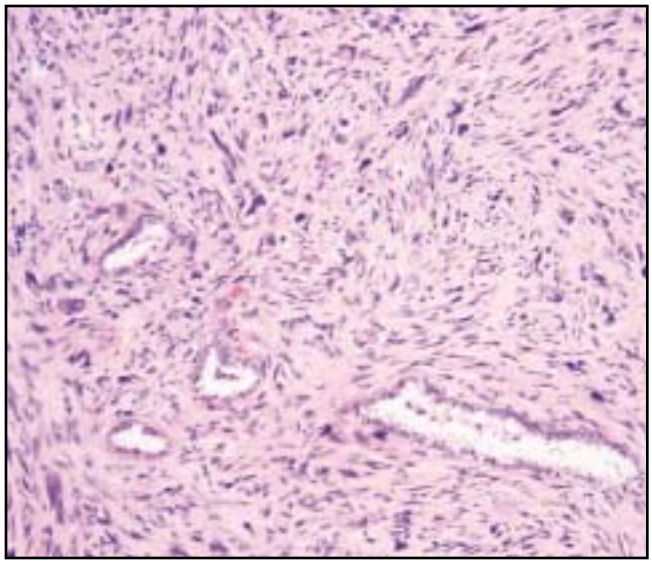

Image 6 Dedifferentiated liposarcoma (high-grade sarcoma) (H&E, ×40).

type. The hyperplastic alveolar epithelium seen around nodules of metastatic ML sometimes was seen at the periphery of DDL nodules.

Clinical Course

In 6 of 8 patients, there were additional multiple lung metastases 10 to 277 months after the initial lung metastasis (Table 8). Metastasis to nonpulmonary sites appeared in 5 patients 0 to 277 months after the appearance of dedifferentiated morphologic features from the primary site or metastasis.

Of 8 patients, 7 had local recurrence 8 to 116 months after the primary diagnosis. All 8 patients had progressive disease, 7 from local recurrence and metastatic disease and 1 from local recurrence only (case 1).

Interval to Pulmonary and Extrapulmonary Metastasis

The appearance of initial lung metastasis from the time of diagnosis of the primary tumor was considerably shorter for PL at 0 to 107 months (mean, 23 months) than for DDL (range, 0-277 months; mean, 51 months) and ML (range, 5-144 months; mean, 53 months) **Table 10**. The occurrence of the first extrapulmonary metastasis also was earlier for PL at 10 to 130 months (mean, 43 months) than DDL (range, 24-277 months; mean, 72 months) and ML (range, 12-158 months; mean, 65 months) (Table 10).

Discussion

In this series of 24 cases of liposarcoma metastatic to the lungs, the majority of patients were male. Although PL and ML cases were distributed randomly among the lung lobes, there was unexplained overrepresentation of the left lung, particularly the left lower lobe, as a site of metastasis for DDL. The lower lobe predilection might be due to increased blood flow to that area,[13,14] but the left laterality is unexplained. In contrast, a large series of melanoma metastatic to the lungs favored the right side over the left.[15]

In all of the metastatic ML to the lungs, the tumor outline was well circumscribed. There were no infiltrating tumor cells at the periphery, and the protruding nests of tumor cells were covered by reactive alveolar epithelium. These changes were interpreted as a sign of a relatively slower tumor growth, thereby permitting some reaction from surrounding tissue. For most ML tumors resected after adjuvant chemotherapy, treatment-related changes such as hypocellularity and extensive hyalinization were prominent. The quantity of cellular areas in ML (RCL) has been used to predict the clinical behavior of ML[3,5,16,17] and proved to be an important prognostic factor. Because these histologic features are based on the primary tumor, it is not known whether they have any meaning if applied to metastatic tumors such as those in the lungs. The cellularity of metastatic ML more often is increased than decreased.[4]

The evaluation of these metastatic tumors is confounded by therapy-related changes precluding the estimation of true cellularity and cytologic appearance of neoplastic cells. Moreover, evidence of therapy-related effects does

Table 10
Liposarcoma With Pulmonary Metastasis: Time to Initial Pulmonary and Extrapulmonary Metastasis and Status at Last Follow-up

	Time to Initial Lung Metastasis		Time to Initial Extrapulmonary Metastasis		
Histologic Type	No. of Cases	Range (Mean), mo	No. of Cases	Range (Mean), mo	Status at Last Follow-up
ML	8	5-144 (53)	5	12-158 (65)	Progressive disease, 5; stable disease, 1; no evidence of disease, 2
PL	8	0-107 (23)	5	10-130 (43)	Progressive disease, 6; stable disease, 1; no evidence of disease, 1
DDL	8	0-277 (51)	5	24-277 (72)	Progressive disease, 8

DDL, dedifferentiated liposarcoma; ML, myxoid liposarcoma; PL, pleomorphic liposarcoma.

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not necessarily translate into better clinical outcome. Two patients in our series had extensive treatment-related changes but had progressive disease. On the other hand, 2 patients with typical ML and cellular ML had not received chemotherapy but were disease-free 10 and 20 months after pulmonary metastasectomy, respectively. These findings suggest that histologically chemotherapy-responsive metastatic ML should be interpreted with caution because disease progression still is possible. Furthermore, it is well known that ML metastasizes to lungs and other organs many years after the diagnosis of primary tumor.[2,3]

Other clinical and pathologic factors shown to influence survival, including location and histologic features of the primary tumor, resectability of the primary and metastatic tumors, length of the disease-free interval, and patient's age, also should be considered when assessing the prognosis.[18-20] The differential diagnosis is of real concern only when the metastatic lesion is solitary and the clinical history is not provided.

The scarcity or absence of viable cells in treated tumors might lead to the consideration of a benign process such as myxoid hamartoma instead of recognition of a treated tumor. In this setting, it is worthwhile to submit additional sections from the tumor to disclose typical areas of ML.

Prominence of myxoid component, a nodular growth pattern, and a uniform population of cells of ML might mimic extraskeletal myxoid chondrosarcoma[21] and epithelioid hemangioendothelioma.[22] Although not a consistent reaction, positivity with S-100 helps in separating ML from extraskeletal myxoid chondrosarcoma and epithelioid hemangioendothelioma.[23] Expression of endothelial markers, including CD31 and CD34 and occasionally cytokeratin, distinguishes epithelioid hemangioendothelioma from ML.[22,24]

ML might be mistaken for low-grade myxofibrosarcoma because of the vascular stroma of the latter.[25] The vessels of low-grade myxofibrosarcoma characteristically are curvilinear, and the cells vary from stellate to spindle, in contrast to the relatively uniform cells of ML.[25] Nonlipogenic cellular ML might be difficult to differentiate from neuroendocrine tumors, melanoma, and the different components of small round cell tumors. The use of cytokeratin, neuroendocrine markers (synaptophysin and chromogranin), HMB-45, MART-1, and lymphoid markers helps categorize these neoplasms.

Cytogenetic study is an important ancillary test. The diagnosis of ML can be suggested by demonstration of t(12;16)(q13;p11) that fuses the *CHOP* and *TLS* genes present in more than 90% of these cases[26,27] or t(12;22)(q13;q12), in which the *CHOP* gene pairs with the *EWS* (Ewing sarcoma) gene present in the remaining 10%.[27]

In view of the pleomorphic, often nonlipogenic histologic features of metastatic PL, primary and other secondary tumors of the lungs such as MFH and spindle cell neoplasms comprised of carcinomas and sarcomas including melanoma enter the wide array of differential diagnoses.[6,23,28] Based on our cases, prolonged disease-free survival is rare for PL after pulmonary metastasectomy. PL has a shorter interval to pulmonary and extrapulmonary metastasis than DDL and ML. Despite excision of primary and metastatic disease and adjuvant treatment, disease progression in terms of metastasis is the usual clinical course. Local recurrence also is common for PLs arising in deep-seated locations such as retroperitoneum and mediastinum.[6,28] The tumor grade and histologic features of primary PL, however, were reported not to affect patient outcome.[28] Most of the lipoblasts of PL and the nonlipoblastic elements to some extent are immunoreactive to S-100 protein.[23,29] Nonlipoblastic differentiation may express expected antigens such as smooth muscle actin and desmin for smooth muscle differentiation, and cytokeratin and epithelial membrane antigen for epithelioid type,[23] but this is not an invariable reaction.[28]

The cytogenetic alterations of PL are multiple and complex,[26] unlike those found in ALT/WDL and DDL and in ML and RCL.[26,27] Recently, a comparative genomic hybridization study detected recurrent chromosomal imbalances with distinct patterns of gains and losses of chromosomes more frequently seen in PL than in DDL.[30] However, these results raise the possibility of not-careful morphologic discrimination between these 2 entities.

All metastatic DDLs in this series had high-grade histologic features, mainly those of an undifferentiated pleomorphic sarcoma, MFH type. A few of the heterologous elements previously described[31] also were present, including rhabdomyosarcomatous and osteosarcomatous differentiation. Because of the similarity with other sarcomas, definitive diagnosis can be established only by clinicopathologic correlation, which is important because DDLs have been reported to follow a less aggressive clinical course than high-grade sarcomas such as PLs and undifferentiated pleomorphic sarcomas (MFH).[7,32-34]

Both PL and DDL tumors have a tendency to involve the lungs more than any other organs in their spread, in contrast to ML, which favors extrapulmonary sites,[3-7,18] including other soft tissue sites and bone. In most of our PL and DDL cases, the tumors in the lung were the first evidence of metastatic disease, and in about half of these cases, the lung was the only site of metastasis. In this series, the PL cases had shorter intervals to lung metastasis than DDL cases, which is in agreement with some published reports.[3,4,6]

Histologically, the aggressive features of metastatic PL and DDL also were noted. Invasive clusters or scattered single neoplastic cells extended into the lung parenchyma at the interface of the tumor and lung parenchyma. Reactive changes such as alveolar hyperplasia that were seen with regularity in ML were noted rarely. Other histologic evidence of aggressiveness

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such as tumor necrosis and vascular invasion also were recognized.[28]

The role of immunohistochemical analysis in the current diagnosis of DDL is limited by the absence of more specific antibodies. Cytogenetic studies have been instrumental in elucidating the relationship of ALT and DDL. The most common abnormalities detected in these lesions are ring and giant marker chromosomes from the q13-15 region of chromosome 12.[27,35,36] Amplification of this region in DDLs has been demonstrated by comparative genomic hybridization,[37] as have genes (*MDM2* and *cdk4*) located in this region by quantitative polymerase chain reaction[38] and immunohistochemical analysis.[39] Because some undifferentiated pleomorphic sarcomas (MFH) might express MDM2 and cdk4, it is not settled whether these markers are shared by those sarcomas or whether tumors with MFH histologic features are derivatives of ALT/DDL.[37,40] The usefulness of cytogenetic and molecular studies is hampered by the long turnaround time, the laborious technical aspects of the procedure, and the need for highly trained personnel to carry out and interpret the test,[28] but it might be essential in cases with equivocal histologic features.

The morphologic features of liposarcoma metastatic to the lungs seem diverse but usually within the spectrum of the histologic type of the primary tumor. For MLs, they are within the range of the typical and cellular type of ML (RCL). The lung metastases from PL and DDL often are nonlipogenic. Both metastatic disease from PL and DDL generally resembles an undifferentiated pleomorphic sarcoma (MFH type) and sometimes with a specific histologic differentiation, particularly for DDL. The pulmonary metastasis of PL occurs earlier than in DDL, reflecting its worse clinical behavior. Likewise, the histologically infiltrative features of the metastatic foci of PLs and high-grade DDLs underscore the aggressiveness of these tumors. Neoadjuvant chemotherapy might alter the histologic features anticipated from a particular type, usually leading to hyalinization and hypocellularity. Of these 3 types of liposarcomas, ML seems to be the most sensitive. After pulmonary metastasectomy, disease-free survival is infrequent and more often seen in ML cases. Overall, in these subsets of patients, the general trend is progressive disease, metastatic disease for ML and PL with a much shorter interval for PL, and metastatic disease and local recurrence for DDL. In addition, it is important to note that DDL, despite high-grade morphologic features, behaves differently from PL and ML.

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