Primary (De Novo) Dedifferentiated Liposarcoma in the Extremities:
A Multi-Institution Tohoku Musculoskeletal Tumor Society Study
of 18 Cases in Northern Japan

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Objective: Dedifferentiated liposarcomas usually occur in the retroperitoneal space and relatively rarely in the extremities.

Methods: We identified 18 patients with primary dedifferentiated liposarcoma in the extremities from the files of Tohoku Musculoskeletal Tumor Society and analyzed demographics, histologic findings, treatments and prognostic factors. The average follow-up period was 58 months.

Results: The subjects were 12 men and 6 women with a mean age of 65 years. All tumors were in the thigh. Nine patients noticed a rapid enlargement of the long-standing tumor. Histologic subtypes of the dedifferentiated area were undifferentiated pleomorphic sarcoma (n = 12), osteosarcoma (n = 2), rhabdomyosarcoma (n = 2), leiomyosarcoma (n = 1) and malignant peripheral nerve sheath tumor (n = 1). In the patient with rhabdomyosarcoma-like dedifferentiated area, extensive necrosis was observed after the preoperative chemotherapy. One patient who underwent marginal excision developed a local recurrence, but inadequate surgical margin was not associated with a risk of local recurrence. Three patients had lung metastasis at initial presentation, and four other patients developed lung metastases during the follow-up period. The overall survival rate was 61.1% at 5 years. On univariate analyses, large size of the dedifferentiated area (> 8 cm), high MIB-1-labeling index (> 30%) for the dedifferentiated area and lung metastasis at initial presentation were significantly associated with poor prognosis.

Conclusions: Primary dedifferentiated liposarcoma in the extremities predominantly occurred in the thigh and a rapid enlargement of long-standing tumors was a characteristic symptom. Although the local behavior of these tumors was less aggressive than that of retroperitoneal dedifferentiated liposarcomas, they had a relatively high metastatic potential.

Key words: pathology – orthopedics/sarcoma – prognostic factors

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INTRODUCTION

The concept of dedifferentiated liposarcoma (DDL) was introduced in 1979 by Evans (1), and DDL was defined as a tumor containing atypical lipomatous neoplasm/well-differentiated liposarcoma (WDL) juxtaposed to a high-grade non-lipogenic sarcoma. Later, the definition of DDL was expanded to WDL with almost entirely comprising low-grade dedifferentiation areas (2). Unlike many other types of sarcomas, DDLs are usually located in the retroperitoneum, and the most important prognostic factor is anatomic location, with retroperitoneal lesions having the worst clinical behavior due to difficulties of complete excision (2–4).

Although orthopedic oncologists occasionally encounter primary DDLs in the extremities, clinicopathologic details and prognostic factors remain to be clarified since the number of those is limited (3,5–13). In this study, we evaluated the clinicopathologic features of 18 patients with primary (de novo) DDL in the extremities at eight oncology centers in northern Japan. We focused on the therapeutic strategy and prognostic impact of dedifferentiation of primary lesions.

PATIENTS AND METHODS

Seven oncology centers in Tohoku Musculoskeletal Tumor Society (TMTS) and National Cancer Center in Tokyo participated in this retrospective collaborative study. Patients with DDL of the extremities who had been treated between 1994 and 2008 were identified from the medical records. Demographics, including gender, age, duration and/or symptoms, were reviewed from clinical records. Magnetic resonance (MR) images were used to evaluate signal intensity, size and depth of the tumors. Chest radiographs and computed tomographic images of the chest and abdomen were examined to determine distant metastasis at initial presentation or follow-up. The margins of surgical excision were classified as adequate (wide margin) or inadequate (intraleisional or marginal margin), according to the definition of Enneking (14).

Gross features of the tumors were reviewed using surgical specimens or their photos. The hematoxylin- and eosin-stained slides of the tumors were reviewed by an expert pathologist (T.H.). Although dedifferentiation may be observed during recurrence of a preexisting WDL (secondary dedifferentiation) (3), to clarify the prognostic impact of dedifferentiation of primary lesions, cases with secondary dedifferentiation were excluded.

The representative blocks of formalin-fixed, paraffin-embedded tissues of the dedifferentiated area (high-grade area) were cut in a 4-μm-thick sections and examined after labeling by using the streptavidin–biotin method with an appropriate use of negative controls throughout and after pre-treatment with heat-induced epitope unmasking. Unmasking was conducted in 10 mM citrate buffer, pH 6.0, in an autoclave at 121°C for 10 min. Primary antibodies for MIB-1 (1:500, Dako, Tokyo, Japan), vimentin (1:200, Dako), S-100 (1:2000, Dako), desmin (1:100, Dako), α-smooth muscle actin (1:100, Dako), muscle-specific actin (1:100, Enzo, NY, USA), myogenin (1:100, Dako) and CD-56 (1:200, Nihonkayaku, Tokyo, Japan) were applied in all 18 cases. The MIB-1-labeling index was estimated by counting the percentage of cell nuclei that stained positive per 100 tumor cells in the region of the tumor with the greatest density of staining. The percentage of cells expressing nuclear staining was analyzed as a continuous variable. Tumors showing >30% staining were classified as 2(+) and tumors with <30% staining were classified as (+).

The latest follow-up information was obtained from physicians of affiliated institutions. The average follow-up period for the 18 patients was 58 months (range: 2–173 months), and for surviving patients, it was 89 months (range: 37–173 months). Survival rate was estimated using the Kaplan–Meier method. The prognostic significance of the following variables on survival was determined using the log-rank test: gender (male or female), history of a prompt enlargement (yes or no), maximum tumor size (larger than mean value or smaller), maximum diameter of the dedifferentiated area (larger than mean value or smaller), lung metastasis at initial presentation, chemotherapy, radiotherapy, surgical margin of the initial surgery (adequate or inadequate), histologic diagnosis of the dedifferentiated area (undifferentiated pleomorphic sarcoma or others) and MIB-1-labeling indexes of the dedifferentiated area (≥30 or <30%). Similarly, risk factors for local recurrence were estimated in 17 patients who underwent surgery. A probability value <0.05 was considered significant. All protocols were approved by the Institutional Review Board at our institutions. Informed consent was obtained from all patients.

RESULTS

The subjects were 12 men and 6 women. Their age at diagnosis ranged from 47 to 86 years (average, 65 years). All 18 tumors were located in the thigh. Seventeen of the 18 tumors were located in layers deeper than the fascia, and the remaining 1 tumor was located in the subcutaneous tissue. Fourteen patients (78%) complained of a mass without pain, and four other patients complained of a mass associated with pain around the mass. The duration of symptoms ranged from 1 to 120 months (average, 38 months) in the 13 patients for whom information about the duration was available. Nine (50%) of the 18 patients noticed rapid growth or a change in the consistency of long-standing tumors, from soft to elastic hard. Three (17%) of the 18 patients had lung metastasis at initial presentation.

MR images were available for review for all cases. The largest diameter of tumors ranged from 3 to 30 cm (mean, 17 cm). In the masses, two areas were adjacent to each other with a clear border, and one of them had high signal
intensity both in T1- and T2-weighted images, which indicated a well-differentiated lipogenic tumor. The other area, measured 1–18 cm (mean, 8 cm), showed low signal intensity in T1-weighted images and high signal intensity in T2-weighted images (Fig. 1).

Ten gross specimens or photographs of the tumors were available for review. All 10 tumors consisted of both a yellowish fatty part and a whitish solid part. The borders of these two parts were well defined. Histologic examination indicated that the yellowish fatty part comprised mature lipogenic cells with large, hyperchromatic nuclei and was classified as Grade 1 according to the FNCLCC grading system (15) (Fig. 2a). The whitish solid part showed increased cellularity with nuclear enlargement and hyperchromasia. A considerable amount of necrosis (5–50%) and high mitotic rate (10–20/10 HPF) were observed, and this part was classified as Grade 3, high-grade sarcoma according to the system.

Among the 18 high-grade sarcomas, 12 showed proliferation of pleomorphic cells without any apparent differentiation; this characteristic was similar to that of malignant fibrous histiocytoma (MFH-, undifferentiated pleomorphic sarcoma-) like features (Fig. 2b). Two cases were diagnosed as osteosarcoma on the basis of bone and osteoid formation among atypical and hyperchromatic cells (Fig. 2c). Two other cases showed a proliferation of atypical cells with abundant eosinophilic cytoplasm. These tumor cells showed strong reactivity for vimentin, desmin and myogenin and were diagnosed as having a rhabdomyosarcoma part. One tumor showed marble-like patterns and whorled structures. Since the tumor cells were symmetrically tapered spindle cells with irregular buckled nuclei and were partially positive for S-100, the tumor was diagnosed as a malignant peripheral nerve sheath tumor. The remaining one tumor was diagnosed as leiomyosarcoma on the basis of cigarette-shaped nuclei of the tumor cells and strong immunoreactivity for α-smooth muscle actin and muscle-specific actin. On the basis of the results of the MIB-1-labeling index, nine of the 18 tumors were classified as 2(+) (Fig. 2d), and the other nine tumors were classified as (+).

Initial surgical treatment was performed in 17 of the 18 patients. The remaining one patient did not undergo surgery (Patient no. 5) because of extensive lung metastasis at initial presentation. Surgical margin was estimated as adequate (wide excision) in eight and inadequate in nine (marginal excision, seven; intralesional excision, two) cases. One patient (Patient no. 3) developed a local recurrence 15 months after surgery with a marginal margin.

Three patients (Patient nos. 1, 17 and 18) underwent preoperative chemotherapy and one patient (Patient no. 15) received postoperative chemotherapy. Drugs used to treat other soft tissue sarcomas, such as doxorubicin, ifosfamide, cisplatin and dacarbazine, were used in the current chemotherapy. In Patient no. 1, who had a tumor with a rhabdomyosarcoma-like dedifferentiated area, the effect of the preoperative chemotherapy was clinically evaluated as ‘partial response’, but histologically, diffuse necrosis was observed in the dedifferentiated area (Fig. 3). In Patient nos. 17 and 18, who had tumors with MFH-like dedifferentiated area, effects of preoperative chemotherapy were evaluated as ‘progressive disease’. Pre-operative radiotherapy (20–60 Gy) was administered to six patients, and post-operative radiotherapy (50–60 Gy) was administered to five patients. The effects of preoperative radiotherapy in the six patients were clinically evaluated as ‘no change’ in four and ‘partial response’ in two patients.

Three patients (Patient nos. 5, 13 and 17) had metastatic tumors in the lung at initial presentation. Patient no. 5 was only administered radiotherapy for the primary tumor, and the patient died of the disease 2 months after the initial presentation. Patient nos. 13 and 17 underwent marginal excision with post-operative radiotherapy and/or chemotherapy, and died of the disease 2 and 5 months after the surgery, respectively. Among the other 15 patients, 4 (27%) developed lung metastases in the follow-up period. None of the four patients underwent thoracotomy, and all four patients died of disease at 9, 12, 15 and 24 months after the initial surgery. Clinicopathologic details of the 18 cases are summarized in Table 1.

Figure 1. Magnetic resonance (MR) images of a 55-year-old woman with a lesion in the thigh. T1-weighted image showed a dedifferentiated area with low signal intensity and a well-differentiated liposarcoma (WDL) area with high signal intensity.
Figure 2. (a) Microphotograph of a WDL. Several atypical cells with large and hyperchromatic nuclei were observed [hematoxylin and eosin (H&E), original magnification ×400]. (b) With regard to high-grade sarcomas, 12 of the 18 tumors showed a proliferation of pleomorphic cells without any apparent differentiation, which was compatible with malignant fibrous histiocytoma (MFH-, undifferentiated pleomorphic sarcoma-) like features (H&E, original magnification ×400). (c) Two of the 18 tumors were determined to have osteosarcoma-like features because of bone and osteoid formation among atypical and hyperchromatic cells (H&E, original magnification ×400). (d) Microphotograph of the dedifferentiated area showing high MIB-1-labeling index.

Figure 3. MR images and microphotographs before (left) and after (right) chemotherapy in Patient no. 1, who had a tumor with a rhabdomyosarcoma-like dedifferentiated area (arrowheads). Histologically, diffuse necrosis was observed in the dedifferentiated area.
### Table 1. Clinical and pathologic details on the 18 patients with primary dedifferentiated liposarcoma in the extremities

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<th>Rec</th>
<th>Ra (Gy)</th>
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A, age; S, sex; Dura, duration of symptoms; Diam, largest diameter; M1, lung metastasis at the initial presentation; Surg, surgical margin; Rec, recurrence; Ra, radiation; Ch, chemotherapy; Dediff, dedifferentiated area; MIB-1, MIB-1-labeling index; Prog, prognosis; F-up, follow up; F, female; W, wide; Rhabdo, rhabdomyosarcoma; NED, no evidence of disease; NA, not available; MFH, malignant fibrous histiocytoma; M, marginal; DOD, died of disease; M, male; MPNST, malignant peripheral nerve sheath tumor; OS, osteosarcoma; I, intrallesional.

**Figure 4.** (a) Overall survival rate of the 18 patients with primary dedifferentiated liposarcoma in the extremities was 61.1% at 5 years (95% confidence interval, 38.6–83.6%). Univariate analysis revealed that (b) large diameter of the dedifferentiated area (>8 cm), (c) high MIB-1 index of the dedifferentiated area (30%) and (d) lung metastasis at initial presentation (M1) were significantly associated with poor prognosis. (b) Less than 8 cm, small diameter of the dedifferentiated area (n = 10); >8 cm, large diameter, (n = 8). (c) Less than 30%, low MIB-1 index of the dedifferentiated area (n = 10); 30%, higher MIB index (n = 8). (d) M0, no metastasis at initial presentation (n = 15); M1, lung metastasis at initial presentation (n = 3).
Univariate analysis revealed that for the 17 patients who underwent surgery, none of the variables, including age, sex, size, symptom, histology, amount of dedifferentiated area, MIB-1-labeling index, metastasis at initial presentation, chemotherapy, radiotherapy or surgical margin was associated with local recurrence.

The overall survival rate of the 18 patients was 61.1% at 5 years (95% CI, 38.6–83.6%; Fig. 4a). Univariate analysis revealed that large diameter of the dedifferentiated area (<8 vs. >8 cm, 80.0 vs. 37.5%; Fig. 4b), high MIB-1 index of the dedifferentiated area (<30 vs. >30%, 80.0 vs. 37.5%; Fig. 4c) and lung metastasis at initial presentation (M0 vs. M1, 0 vs. 73.3%; Fig. 4d) were significantly associated with a poor prognosis. There was no significant association between survival and the variables, including age, gender, symptom, maximum tumor size, histology, surgical margin, radiation and chemotherapy.

**DISCUSSION**

To our knowledge, 21 cases of primary DDLs occurring in the extremities have been reported in the literature (3,5–13). Of these, except the case of an 8-year-old girl (13), all occurred in persons aged over 50 years (age range: 52–83 years), and the patients were predominantly men (men, 14; women, 7). The current study showed similar age and gender distributions. The most peculiar demographic feature was the predominant occurrence of the condition in the thighs. Seventeen (81%) of the 21 cases reported in the literature and all 18 cases in this study showed occurrence of the tumor in the thigh, although the reason for this predominance is not known.

The current 18 patients tended to complain of rapid growth or changes in the consistency of long-standing tumors; however, these symptoms have not been mentioned in the previous literature. Since dedifferentiation is considered to be time-dependent (4,16), rapid growth or changes in the consistency of long-standing tumors may be a clinical sign of dedifferentiation. We should consider the possibility of DDL if an elderly patient with a lipogenic and long-standing mass in the thigh complains of rapid enlargement or change in the consistency of the mass.

In this study, lung metastasis at initial presentation was a risk factor. A systemic survey using modern imaging techniques is essential for the staging of sarcomas. With regard to pathologic features, large size (>8 cm) and high MIB-1 index of the dedifferentiated area (>30%) correlated with poor prognosis. Hasegawa et al. (17) reported the usefulness of the MIB-1-labeling index for his new grading system of soft tissue sarcomas. The MIB-1-labeling index of the 18 cases was determined according to their categories (<30 or ≥30%). Although a high MIB-1 rate was found to be a significant factor affecting survival in many types of sarcomas, the implications of a high MIB-1 rate for primary DDL in the extremities have not been well discussed. Therefore, if the size of the dedifferentiated area is more than 8 cm and the MIB-1-labeling index in a biopsy specimen obtained from a dedifferentiated area is higher than 30%, a new treatment strategy might be considered. Our study with considerably long follow-up clarified that the condition has a relatively aggressive clinical course; 7 of the 18 patients died of the disease, although previous literature on DDL has stressed poor prognosis of retroperitoneally located tumors and less aggressiveness of DDL in the extremities (2,4). Therefore, careful attention during the follow-up period is important in cases of DDL in the extremities.

Preoperative chemotherapy was administered to three patients in the current series. Only one of the three patients with tumors with a rhabdomyosarcoma-like dedifferentiated area showed severe necrosis in the surgical specimen; good results were obtained for this case. In the other two cases with an MFH-like dedifferentiated area, the effect of the chemotherapy was not apparent, and both patients died of the disease. Post-operative chemotherapy was administered to one patient with a tumor with a rhabdomyosarcoma-like dedifferentiated area, and at recent follow-up, this patient showed a good clinical result. Therefore, chemotherapy for primary DDL in the extremities may be valuable when the dedifferentiated area has rhabdomyosarcoma-like features. However, the usefulness of radiation therapy for local control remains controversial. In the current series, four patients were treated with pre-operative radiotherapy, and its effects were clinically evaluated as ‘no change’ in one and ‘partial response’ in three patients. In addition, univariate analysis showed no relationship between radiation therapy and local recurrence. Therefore, the usefulness of radiation therapy for the local control of primary DDL of the extremities should be investigated further.

The relationship between local recurrence and surgical margin was unclear from the current statistical analyses. Only one of the nine patients who underwent surgery with inadequate (marginal or intralesional) margin developed local recurrence, and no patient developed local recurrence after surgery with adequate (wide) margin. Although wide excision may be associated with good local control, clinical results after marginal excision of primary DDL of the extremities were also acceptable. In the case (Patient no. 3) with local recurrence after the surgery, the dedifferentiated area was located on the surface of the tumor and the surgical margin at the dedifferentiated area was inadequate. On the other hand, in seven of the nine cases without local recurrence, surgical margin at the WDL area was inadequate. Hoshi et al. reported one case resected with a marginal margin at the WDL portion. Since this patient has been continuously disease-free for 19 months after the surgery, the authors considered a marginal margin or better can be considered safe only for the WDL part (12). Further study regarding a surgical margin of DDL should be separately evaluated for the WDL area and dedifferentiated area.

In conclusion, primary (de novo) DDLs in the extremities predominantly occur in the thighs of elderly men, and a
rapid growth or change in the consistency of a long-standing tumor is a characteristic symptom. The clinical behavior of these tumors is relatively aggressive, and initial presentation includes lung metastasis, large size and a high MIB-1-labeling index at the dedifferentiated area are related with poor prognosis. Wide excision is a reliable procedure for local control of the dedifferentiated area, but for the WDL area, clinical results after marginal excision were also acceptable. Chemotherapy might be indicated for cases with a rhabdomyosarcoma-like dedifferentiated area, but the effectiveness of chemotherapy for other types is unclear.

**Conflict of interest statement**
None declared.

**References**