Atypical Lipomatous Tumors/Well-differentiated Liposarcomas: Clinical Outcome of 67 Patients

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abstract

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Atypical lipomatous tumors/well-differentiated liposarcomas are low-grade malignant mesenchymal neoplasms with high propensity to local recurrence and potential to dedifferentiate to higher grades over time. However, the published risks of local recurrence and dedifferentiation vary, and no unified treatment and follow-up plan has been accepted. We performed a study to evaluate the long-term clinical behavior and proper treatment and follow-up strategy for these tumors. We retrospectively reviewed the files of 101 patients treated between 1990 and 2008 with the diagnosis of atypical lipomatous tumors/well-differentiated liposarcomas. For 67 of these patients, complete data and 2-year minimum follow-up were available and were included in the study; 47 patients (group A) had primary surgical treatment at our institution and 20 patients (group B) were referred after ≥1 local recurrences. Mean follow-up was 81 months (range, 24-229 months). The local recurrence rate of primary atypical lipomatous tumors/well-differentiated liposarcomas was 10.6% (5/47 group A patients). The local re-recurrence rate of the recurrent atypical lipomatous tumors/well-differentiated liposarcomas was 52% (13/67 group A and B patients). Recurrences developed as late as 140 months after diagnosis and treatment. The rate of dedifferentiation at recurrences was 4% (1/25 group A and B patients with recurrent tumors). No patients developed metastases. Atypical lipomatous tumors/well-differentiated liposarcomas are associated with an increased rate of local re-recurrence and low risk of dedifferentiation at recurrences. Long-term follow-up is recommended for early diagnosis and treatment of local recurrences.
Atypical lipomatous tumors/well-differentiated liposarcomas are low-grade, slow-growing, locally aggressive malignant mesenchymal neoplasms composed entirely or in part of a mature adipocytic proliferation showing significant variation in cell size, and at least focal nuclear atypia in both adipocytes and stromal cells. They account for 40% to 45% of all liposarcomas and are usually diagnosed after the fifth decade of life; slight male predominance has been reported.

Atypical lipomatous tumors/well-differentiated liposarcomas are synonyms describing lesions identical morphologically, karyotypically, and in terms of biologic behavior. Use of the term atypical lipomatous tumor is determined principally by tumor location and resectability. The fact that well-differentiated liposarcomas show no potential for metastasis unless they undergo dedifferentiation led, in the late 1970s, to the introduction of terms such as atypical lipoma or atypical lipomatous tumor, particularly for lesions arising at surgically amenable locations in the limbs and trunk, because at these sites, wide excision should usually be curative and hence the designation sarcoma is not warranted. However, in retroperitoneal and mediastinum locations, it is often impossible to obtain a wide surgical excision; well-differentiated liposarcomas in these locations have been associated with adverse prognosis and a higher rate of local recurrence (often repeated and ultimately uncontrolled), and dedifferentiation of recurrent tumors.

Therefore, it has been advocated that the term well-differentiated liposarcoma be retained for retroperitoneal/mediastinal tumors and atypical lipomatous tumors for the rest. Histologically, atypical lipomatous tumors/well-differentiated liposarcomas are composed of mature adipocytic cells, atypical stromal cells, and a limited number of scattered lipoblasts. A limited component of fibrous or myxoid tissue is also consistent with this diagnosis. Many authors have reported that the cut-off portion of myxoid and fibrous areas with higher mitotic rate and cellularity is uncertain. This portion has been regarded to be 1 cm (up to 3 cm in large tumors) and is considered as a sign of low-grade dedifferentiation from the beginning. Similarity to large deep-seated lipomas is also a diagnostic problem. Several authors have proposed a positivity in overexpression of MDM2, HMGA2, and CDK4 as a reliable hallmark to distinguish between these 2 entities and genetic differences between low- and higher-grade liposarcomas. Others have reported that CDK4 in atypical lipomatous tumors/well-differentiated liposarcomas is expressed inconsistently and is associated with adverse prognosis compared to the MDM2/CDK4 genotype.

The optimal treatment, the need for adjuvant radiation therapy, the rate of local recurrence, and the adequacy of follow-up for atypical lipomatous tumors/well-differentiated liposarcomas have been uncertain. This article presents a series of patients with atypical lipomatous tumors/well-differentiated liposarcomas of somatic sites, excluding retroperitoneal and mediastinum, with the purpose of clarifying the long-term clinical behavior of these tumors, the optimal treatment, whether radiation therapy is needed, and how long these patients should be followed.

Materials and Methods

We retrospectively studied the files of 101 patients with atypical lipomatous tumors/well-differentiated liposarcomas of somatic sites admitted and treated at our institution between 1990 and 2008. Thirty-four patients were excluded because of retroperitoneal or mediastinum location, histological findings of cellular myxoid areas and foci of dedifferentiation, follow-up <2 years, or being lost to follow-up. The remaining 67 patients were included in this study.

Thirty-five men and 32 women had a mean age of 60 years (range, 34-75 years). The most common location was the thigh (50 patients), followed by the popliteal fossa (5 patients), the pelvic girdle (4 patients), the arm (2 patients), and the dorsum of the thoracic and abdominal wall, leg, forearm, hand, and neck (1 patient each). The most common presenting symptom (62 patients) was a slow-growing mass (Figure 1); 12 of these patients reported additional pain (Figure 2). Mean tumor size at diagnosis was 19 cm (range, 3-40 cm). One patient with a large (40 cm) tumor at the posterior thigh presented with skin ulceration and peroneal nerve palsy from pressure effect (Figure 3). Forty-nine patients had histological diagnosis of lipoma-like liposarcomas, 9 patients of sclerosing liposarcomas, and 9 with areas of both subtypes; no other subtype was observed (Figure 4). No patient had distant metastasis at diagnosis. Mean follow-up of the 67 patients was 81 months (range, 24-229 months). All patients or their families gave written informed consent to be included in this study. This study was approved by the Institutional Review Board/Ethics Committee of our institution.

The 67 patients were divided into 2 groups (Table 1). Group A comprised 47 patients who had primary diagnosis and treatment at our institution. In group A, the incidence of local recurrence and type of surgery in primary atypical lipomatous tumors/well-differentiated liposarcomas was evaluated. Group B comprised 20 patients who were referred to our institution for recurrence of histologically confirmed atypical lipomatous tumors/well-differentiated liposarcomas. Eight of the 20 patients in group B had >2 local recurrences at a mean of 62 months (range, 26-120 months) before referral; 4 patients had 2, two patients had 3, and 2 patients had 4 local recurrences. Group B patients were included in this study to increase the sample size and evaluate the risk of local re-recurrence and dedifferentiation of recurrent atypical lipomatous tumors/well-differentiated liposarcomas. All patients with recurrent tumors were treated at...
RESULTS

The local recurrence rate of the primary atypical lipomatous tumors/well-differentiated liposarcomas was 10.6%; five of the 47 patients in group A had local recurrence at a mean of 73 months (range, 18-140 months) after primary surgery. The mean size of the recurrent tumors was 19 cm (range, 12-23 cm). Three of the 5 recurrent tumors had initial histological diagnosis of lipoma-like subtype and 2 had mixed lipoma-like/sclerosing subtype. Four of the 5 patients with recurrence had marginal and 1 intrallesional excision, and all 5 patients had postoperative radiation therapy after the primary surgery (Table 2).

The local re-recurrence rate of the total recurrent atypical lipomatous tumors/well-differentiated liposarcomas was 52%; 13 patients (1 in group A and 12 in group B) with recurrent tumors had a re-recurrence at a mean of 39 months (range, 4-108 months) after re-excision for the first local recurrence, even if with wide margins. All of these patients had marginal excision at primary surgery. Eight of the 12 patients in group B had >2 local recurrences before referral, and 4 had re-recurrence after re-excision at our institution. The mean size of the re-recurrent tumors was 17 cm (range, 8-23 cm). All patients with local recurrences were treated with re-excision with wide margins.

The rate of dedifferentiation at recurrences was 4% (1 in 25 group A and B patients with recurrent tumors). Dedifferentiation to round-cell liposarcoma was observed in 1 patient in group A with a recurrent tumor at 72 months, which was initially histologically diagnosed as lipoma-like atypical lipomatous tumor/well-differentiated liposarcoma. This patient was treated with re-excision and brachytherapy without local recurrence. No patient in group B had dedifferentiation at recurrences. No patient of this series had metastases during the study period.

DISCUSSION

Controversy exists regarding the rate of local recurrence, dedifferentiation, optimal treatment, and adequate follow-up time for atypical lipomatous tumors/well-differentiated liposarcomas.2,4,7,8,19-24 Different local recurrence and re-recurrence rates have been previously reported, rang-
Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Age (Range), y</th>
<th>Histology, No.</th>
<th>Margins at Primary Surgery, cm</th>
<th>Radiation Therapy, No.</th>
<th>Mean Follow-up (Range), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n=47)</td>
<td>61.2 (34-42)</td>
<td>LL=32, SC=6, L/S=9</td>
<td>Wide=8, Marginal=36</td>
<td>7a</td>
<td>86 (24-196)</td>
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<tr>
<td>B (n=20)</td>
<td>55 (35-75)</td>
<td>LL=17, SC=3, L/S=11</td>
<td>Wide=9, Marginal=9</td>
<td>3b</td>
<td>79 (43-147)</td>
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<tr>
<td>Total (n=67)</td>
<td>60 (34-75)</td>
<td>LL=49, SC=9, L/S=49</td>
<td>Wide=19, Marginal=45</td>
<td>10</td>
<td>81 (24-229)</td>
</tr>
</tbody>
</table>

Abbreviations: LL, lipoma-like; L/S, mixed lipoma-like and sclerosing; SC: sclerosing.
aAfter primary surgery: 3 patients with intralesional margins and 4 patients with contaminated marginal margins.
bAfter primary surgery.

Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Age (Range), y</th>
<th>Histology, No.</th>
<th>Margins at Primary Surgery, No.</th>
<th>Radiation Therapy, No.</th>
<th>Local Recurrence</th>
<th>Local Re-recurrence</th>
<th>Dedifferentiation, No.</th>
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<tr>
<td>A (n=5)</td>
<td>57.2 (42-70)</td>
<td>LL=3, L/S=2</td>
<td>Marginal (4), intralesional (1)</td>
<td>5</td>
<td>5/47 (10.6%)</td>
<td>1/25 (4%)</td>
<td>LL to RC (1)</td>
</tr>
<tr>
<td>B (n=20)</td>
<td>51.5 (40-57)</td>
<td>LL=20, L/S=0</td>
<td>Wide (11), marginal (9)</td>
<td>3</td>
<td>20b</td>
<td>12b</td>
<td>44</td>
</tr>
<tr>
<td>Total (n=25)</td>
<td>56 (40-70)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>5/47 (10.6%)</td>
<td>13/25</td>
<td>39</td>
</tr>
</tbody>
</table>

Abbreviations: LL, lipoma-like; L/S, mixed lipoma-like and sclerosing; RC, round cell liposarcoma.
aTwelve of 20 patients had 1 local recurrence, and 8 of 20 patients had >2 local recurrences before referral (4 had 2, two had 3, and 2 had 4 local recurrences).
bEight of 12 patients had >2 local recurrences before referral, and 4 of 12 patients had local re-recurrence after re-excision at our institution.

Table 3

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Patients</th>
<th>LR No.</th>
<th>LR %</th>
<th>LRR No.</th>
<th>LRR %</th>
<th>Dedifferentiation No.</th>
<th>Dedifferentiation %</th>
<th>Unicentric Study (No. of Primary/Referred Patients)</th>
<th>Mean Follow-up, mo</th>
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<tr>
<td>Billing et al2</td>
<td>38</td>
<td>4/38</td>
<td>10</td>
<td>0/4</td>
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<td>0/38</td>
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<td>Weiss and Rao7</td>
<td>46</td>
<td>20/46</td>
<td>43</td>
<td>12/20</td>
<td>60</td>
<td>3/46</td>
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<td>Evans8</td>
<td>61b</td>
<td>1/11b</td>
<td>9</td>
<td>1/1</td>
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<td>0/11</td>
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<td>8</td>
<td>2/5</td>
<td>40</td>
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<td>Lucas et al21</td>
<td>58b</td>
<td>14/58</td>
<td>24</td>
<td>10/14</td>
<td>71</td>
<td>6/58</td>
<td>10</td>
<td>Yes (12/46b)</td>
<td>112</td>
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<td>Rozental et al22</td>
<td>31</td>
<td>16/31</td>
<td>52</td>
<td>7/16</td>
<td>44</td>
<td>4/31</td>
<td>13</td>
<td>Yes (22/9)</td>
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<tr>
<td>Basset et al23</td>
<td>51</td>
<td>14/51</td>
<td>27</td>
<td>5/14</td>
<td>35</td>
<td>1/51</td>
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<td>3/11</td>
<td>27</td>
<td>3/3</td>
<td>100</td>
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<td>Yes (8/3)</td>
<td>18</td>
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<td>5/47c</td>
<td>10.6</td>
<td>13/25d</td>
<td>52</td>
<td>1/25d</td>
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<td>Yes (47/20)</td>
<td>81</td>
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<tr>
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<td>25</td>
<td>41/82</td>
<td>50</td>
<td>10/327</td>
<td>3</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

aIncluded all sites of atypical lipomatous tumors/well-differentiated liposarcomas.
bTumors of the extremities.
cForty-seven patients with primary tumors (group A).
dTwenty-five patients with recurrent tumors (groups A and B).
The risk for dedifferentiation of atypical lipomatous tumors/well-differentiated liposarcomas is 4%. In this study, we reviewed a series of patients with atypical lipomatous tumors/well-differentiated liposarcomas to evaluate the risk for recurrent tumors. We identified 2 limitations to this study. First, we did not include group B patients in the evaluation of local recurrence rate after primary surgery because we are not aware of the total number of patients with these tumors treated elsewhere but only of the number of patients referred to our hospital for recurrence. Second, although this was a large series with long-term follow-up, the number of patients is still too small to draw powerful conclusions. Although the mean follow-up time of 81 months in the present series exceeds the mean time to local recurrence of 73 months as evaluated for the primary tumors, it is likely that more local recurrences will occur with further follow-up.

A statistically significant correlation between positive surgical margins and risk of recurrence for atypical lipomatous tumors/well-differentiated liposarcomas has been reported. Because it is often difficult to obtain wide margins due to the large tumor size and proximity to major nerves and vessels, marginal excision can be justified; however, intralesional surgery should be avoided. Because these lesions are often lobulated, they tend to form internal hernias (Figure 5) that can mislead the surgeon and accidentally leave part of the tumor behind unwittingly performing intralesional surgery. The role of radiation therapy for atypical lipomatous tumors/well-differentiated liposarcomas is unclear. Some consider that adjuvant radiation therapy can reduce the risk of local recurrence, but others are concerned that this may potentiate dedifferentiation to a higher grade in case of recurrence. In the present series, of the 5 group A patients with recurrent tumors, 4 had marginal and 1 had intralesional primary surgery, and all had postoperative radiation therapy. The most important finding of this study is that recurrent tumors have a high risk of local re-recurrence, even if wide margins re-excision for recurrences is performed. This stresses the importance of an adequate, wide-margin primary excision for atypical lipomatous tumors/well-differentiated liposarcomas. Although we cannot document if radiation therapy may be associated with dedifferentiation, we can conclude that radiation therapy is not useful for local tumor control. The low risk for dedifferentiation of atypical lipomatous tumors/well-differentiated liposarcomas (4%) found in this series is in line with the literature. Several authors have suggested that atypical lipomatous tumors/well-differentiated liposarcomas are a continuum entity with slow propensity to dedifferentiate, but with a tendency to metastasize after dedifferentiation occurs. Dedifferentiation is a time- rather than a size-dependent factor; although the reported rate of dedifferentiation widely ranges from 0% to 13%, one should keep in mind that the risk of dedifferentiation exists with recurrent atypical lipomatous tumors/well-differentiated liposarcomas.

Previous studies have proposed a minimum posttreatment follow-up of 5 years, while others have suggested no follow-up at all. We do not concur with these suggestions because, according to the results of the present study, recurrences as late as 140 months may occur, with a mean time to local recurrence of 73 months (6 years). Therefore, we recommend that all patients with atypical lipomatous tumors/well-differentiated liposarcomas, and especially those with recurrent tumors, be seen routinely after diagnosis and treatment for a follow-up period of 6 years.

REFERENCES

1. Laurino L, Furlanetto A, Orvieto E, Dei Tos AP. Well-differentiated liposarcoma (atypi-


17. Italiano A, Bianchini L, Keslar F, et al. HMGA2 is the partner of MDM2 in well-differentiated and dedifferentiated liposarcomas whereas CDK4 belongs to a distinct inconsistent amplicon. Int J Cancer. 2008; 122(10):2233-2241.


