ABSTRACT

Cytogenetic study of short-term cultures from 10 adipose tissue tumors (eight lipomas, one myxoid liposarcoma, and one mixed liposarcoma) have revealed clonal chromosome abnormalities in seven cases. In both malignant tumors, translocation (12;16) was the sole aberration, and in the mixed liposarcoma, the breakpoints could be sublocalized to bands 12q13.3 and 16p11.2, thus confirming findings of Eneroth et al., Cancer Genet. Cytogenet., 48: 101-107, 1990. Three lipomas displayed predominantly normal karyotypes; in a fourth case, the karyotype 44,XX,-6,der(7)(t(6;7)(p21.3-22;p22))ins(7)(p22q11.2q22),-13 was found. Four remaining lipomas were characterized by structural rearrangements of chromosome 12. We were able to achieve high resolution banding patterns in two tumors with translocations (3;12)(q28;q15) and (1;2)(p36;q13;q15). In both of these cases, the chromosome 12 breakpoint could be unequivocally assigned to band q15. Similarly, band 12q15 was also rearranged in two other lipomas with translocations (12;16)(q15;q32) and (12;20)(q15;q13.1). Our results support the hypothesis that the chromosome 12 breakpoint in lipomas is located more distally than the breakpoint in myxoid liposarcomas and some other soft-tissue malignant neoplasms and that it is cytogenetically identical with breakpoints detected in such benign tumors as uterine leiomyoma and pleomorphic adenoma of the salivary gland.

INTRODUCTION

Cytogenetic studies of lipomas, benign tumors of adipose tissue, have shown that clonal chromosome aberrations are present in about 50% of >250 cases analyzed to date. The most consistent finding has been the recombination of the region 12q13-15 with various chromosomes, particularly often with chromosome 3 as t(3;12)(q27-28;q13-14) (1-3). Nonrandom involvement of the long arm of chromosome 12, in the form of a translocation (12;16)(q13;p11), is also characteristic for some types of malignant lipogenic neoplasms, namely, myxoid and mixed liposarcoma (4). However, since the original description of 12q13-14 rearrangements in lipoma (5, 6) and myxoid liposarcoma (7, 8), the question of whether the exact breakpoints in benign and malignant tumors are the same or different remains unanswered. Whereas the chromosome 12 breakpoint in myxoid liposarcoma has been consistently mapped to 12q13, in lipoma breakpoints have been described as 12q13, 12q14, or 12q15 (1-4). Recently, Eneroth et al. (9) sublocalized the myxoid liposarcoma breakpoints to subbands 12q13.3 and 16p11.2. To our knowledge, analogous sublocalization of breakpoints in lipomas with 12q13-15 changes has not been accomplished to date.

We present results of cytogenetic studies performed on 10 adipose tissue tumors. Rearrangements of chromosome 12 were detected in two liposarcomas and four lipomas; in three of these cases, we were able to achieve high resolution banding patterns, indicating that the chromosome 12 breakpoints differed between benign and malignant lesions.

MATERIALS AND METHODS

Ten tumors, eight benign and two malignant, were studied. Basic clinical and pathological data are summarized in Table 1. The tumors of patients 1 and 2 were diagnosed histopathologically as mixed (myxoid with round cell areas) and myxoid liposarcomas, respectively, and cases 3-10 were lipomas.

All lipomas were subcutaneously and all, with the exception of case 8, were solitary.

Nine tumor samples were obtained immediately after surgery; the specimen from case 2 was delivered to the cytogenetic laboratory after having been stored in transporting medium (RPMI 1640 with antibiotics) in a refrigerator at 4°C for 4 days (approximately 90 h). The specimens were processed for cytogenetic analysis as described by Limon et al. (10). In brief, the tissue was minced with scissors and disaggregated in collagenase (200 units/ml) overnight and cultured in RPMI 1640 medium with 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid buffer supplemented with 15% fetal bovine serum, t-glutamine, and antibiotics. After 4-10 days, the cultures were exposed to colcemid, hypotonic solution, and three changes of fixative. The chromosomes were G-banded with trypsin and Wright's stain; in case 10, a method of preparation of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact. 1 Financial support: Coleman Leukemia Research Fund and Grant CA-16056 from NIH.

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The chromosome 12 breakpoints differed between benign and malignant lesions.
Table 1 Clinicopathological and cytogenetic data concerning 10 cases of adipose tissue tumors

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex/age (yr)</th>
<th>Diagnosis(^a)</th>
<th>Location</th>
<th>Size (cm)</th>
<th>No. of cells analyzed</th>
<th>Karyotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M/73</td>
<td>MxLS</td>
<td>Knee</td>
<td>11 x 9 x 6</td>
<td>22</td>
<td>46.XY.t(12;16)(q13.3;p11.2)[21](^b)</td>
</tr>
<tr>
<td>2</td>
<td>M/43</td>
<td>MLS</td>
<td>Thigh</td>
<td>20 x 15 x 7</td>
<td>15</td>
<td>46.XY.t(12;16)(q13.p11)[15]</td>
</tr>
<tr>
<td>3</td>
<td>M/28</td>
<td>L</td>
<td>Neck</td>
<td>7 x 3 x 3</td>
<td>25</td>
<td>46.XY[24](^b)</td>
</tr>
<tr>
<td>4</td>
<td>F/37</td>
<td>L</td>
<td>Buttock</td>
<td>12 x 10 x 5</td>
<td>20</td>
<td>46.XY(13;12)(q28;q15)[20</td>
</tr>
<tr>
<td>5</td>
<td>M/55</td>
<td>L</td>
<td>Hip</td>
<td>12 x 8 x 5</td>
<td>24</td>
<td>46.XY(13;12)(q28;q15)[34−46.XY(t;12;16)(q28;q15),del(3)]</td>
</tr>
<tr>
<td>6</td>
<td>F/48</td>
<td>L</td>
<td>Upper</td>
<td>10 x 10 x 4</td>
<td>16</td>
<td>37−44.XX−6,del(7)(6;7p21.3−22p22)[11p13][7q21.3][cpl9]</td>
</tr>
<tr>
<td>7</td>
<td>F/53</td>
<td>L</td>
<td>Abdomen</td>
<td>9 x 8 x 2</td>
<td>19</td>
<td>40−46.XX(t;12;14)(q15;q32)[cpl9]</td>
</tr>
<tr>
<td>8</td>
<td>M/57</td>
<td>L</td>
<td>Thigh</td>
<td>15 x 9 x 4</td>
<td>26</td>
<td>46.XY(13;12)(q13;q13.1)[cpl9]</td>
</tr>
<tr>
<td>9</td>
<td>F/32</td>
<td>L</td>
<td>Calf</td>
<td>3 x 2 x 1</td>
<td>40</td>
<td>46.XY(13;12)(q13;q13.1)[cpl9]</td>
</tr>
<tr>
<td>10</td>
<td>M/50</td>
<td>L</td>
<td>Shoulder</td>
<td>7 x 4 x 3</td>
<td>41</td>
<td>43−46.XY(t;12;20)(q15;q13.1)[cpl9]</td>
</tr>
</tbody>
</table>

\(^a\) MxLS, mixed liposarcoma; MLS, myxoid liposarcoma; L, lipoma.

\(^b\) The presence of a single cell with abnormalities not described in the karyotype.

DISCUSSION

Cytogenetic analyses of lipoma have led to identification of at least six karyotypically distinct subgroups, characterized by the presence of a normal diploid chromosome complement, structural changes involving 12q13–15, supernumerary ring chromosomes, del(13)(q12q22), aberrations involving 11q13, and rearrangements of 6p21–23 (1–4). Sometimes overlying of cytogenetic subtypes has been noted, with two or even more recurrent abnormalities occurring in the same tumor (3). Our case 6 may serve as an example of such a situation, because both monosomy 13 and a nonreciprocal translocation involving 6p21−22 were found in this tumor. Similarly, in a sideline of case 10, in addition to t(12;20), loss of 13q material due to dic(6;13)(q11;q21) was observed. It is of interest that rearrangements of a region 6p21–23 have also been described in uterine leiomyomas (14), in pleomorphic adenomas of the salivary gland (15), in endometrial polyps (16–18), and in pulmonary chondroid hamartomas (19, 20), suggesting that this region harbors a gene or genes of importance in the development of a wide spectrum of benign lesions.

Four of five karyotypically abnormal lipomas in our series were characterized by translocations between chromosome 12 and other autosomes, confirming previous observations that abnormalities of 12q are the most frequently encountered cytogenetic changes in lipoma. Several chromosomes have been described as 12q translocation partners, but t(12;14) and t(12;20) observed in our cases 7 and 10, respectively, hitherto have not been reported. Thus, the addition of these cases means that only chromosomes 13, 16, 18, 22, and Y have not yet been seen to be involved in translocations with chromosome 12 in lipoma (2, 3).
Fig. 2. Partial karyotypes of three cells (A, B, and C) from the lipoma of case 6 demonstrating der(7)t(6:7)(p21.3–22:p22)ins(7)(p22q11.2:q22) (left) and corresponding schematic presentation (right). Arrows, breakpoints.

Fig. 3. Partial karyotypes of three cells (A, B, and C) representative for the stemline in the lipoma of case 5 illustrating t(3:12)(q28:q15) and t(3:15)(q25.1:q11.2) (left) and corresponding diagrammatic representation (right). Arrows, breakpoints.
The morphology of derivative chromosomes in all cases with 12q rearrangements studied by us clearly demonstrates that the chromosome 12 breakpoint in lipoma is in 12q15. The exact mapping of breakpoints in reciprocal translocations can be cytogenetically difficult, especially when regions which share similar banding features, as in t(3:12)(q27–28;q13–15), are juxtaposed. Thus, inconsistencies in 12q breakpoint assignments in the literature may not reflect true heterogeneity of breakpoints but rather interpretation differences between examiners. Although the possibility that in some lipomas structural aberrations involve 12q14 or 12q13 cannot be ruled out (3, 21), our results indicate that the proportion of lipomas with 12q15 changes is higher than was previously estimated.

Structural aberrations of the long arm of chromosome 12 have also been repeatedly found in such benign tumors as uterine leiomyoma.
and pleomorphic adenoma of the salivary gland. In both of these entities, 12q breakpoints have been predominantly mapped to q14 or q15 (14, 15, 22, 23). A recent high resolution cytogenetic study performed by Pandis et al. (24) showed that the 12q breakpoint in t(12;14), the translocation typical for uterine leiomyoma, is in 12q15. Thus, it is quite possible that the same locus at 12q15 is affected by chromosomal rearrangements in all three benign tumors: lipoma, uterine leiomyoma, and pleomorphic adenoma of the salivary gland.

In myxoid and mixed liposarcomas, however, the chromosome 12 breakpoint has been consistently assigned to 12q13 and never to 12q15 or 12q14. Both liposarcomas studied by us, as well as about 20 tumors reported in the literature (2, 4), displayed the t(12;16) (q13;p11). We were able to sublocalize liposarcoma breakpoints to 12q13.3 and 16p11.2 in one mixed liposarcoma, thus corroborating findings of Eneroth et al. (9). Interestingly, the chromosome 12 breakpoint in another nonrandom aberration, the t(12;22)(q13;q12), that is specific for clear cell carcinoma of tendons and aponeuroses also has been mapped to 12q13 (25–27). Moreover, this band has been rear ranged in a leiomyosarcoma with the t(12;13)(q13;q22) (28), in an alveolar and four embryonal rhabdomyosarcomas (29, 30), in two malignant hemangiopericytomas (31), and in four chondrosarcomas (32–34). On the other hand, a benign chondroma studied by Mandahl et al. (33) had a complex four-way translocation (X;12;8;13) with the breakpoints in myxoid liposarcoma and lipoma are different.

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**ADDENDUM**

After submission of our article, Aman et al. (35) described rearrangements of the CHOP gene, which maps to 12q13, in all nine myxoid liposarcomas studied and in none of the seven lipomas with cytogenetic changes of the region 12q13–15. These findings support our conclusion that chromosome 12 breakpoints in myxoid liposarcoma and lipoma are different.

**REFERENCES**


Fig. 6. Partial karyotypes of two cells (A and B) from the lipoma of case 7 demonstrating t(12;14) (q13;p12) (left) and corresponding schematic representation (right). Arrows, breakpoints.

**LOCALIZATION OF LIPOMA AND LIPOSARCOMA BREAKPOINTS**


Chromosome 12 Breakpoints Are Cytogenetically Different in Benign and Malignant Lipogenic Tumors: Localization of Breakpoints in Lipoma to 12q15 and in Myxoid Liposarcoma to 12q13.3

Krzysztof Mrózek, Constantine P. Karakousis and Clara D. Bloomfield


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