Chromosomal evolution and tumor progression in a myxoid liposarcoma

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A myxoid liposarcoma showed macroscopic, histologic, and cytogenetic heterogeneity. In one of three myxoid nodules and in the surrounding lipoma-like tumor tissue, the translocation t(12;16)(q13;p11), known to be specific for myxoid liposarcoma, was found as the sole chromosomal abnormality. In the other two nodules, additional rearrangements involving chromosomes 1, 12, and 16 were found. These aberrations were probably secondary to the primary t(12;16), and are cytogenetic evidence of clonal evolution. The complex chromosome aberrations were present in those tumor parts that had more malignant histology, indicating that the acquisition of secondary chromosomal aberrations parallels the histologic manifestations of tumor progression.

Nonrandom chromosomal aberrations are a feature of neoplastic cells. This has been shown both for hematologic malignancies and, in later years, for benign and malignant solid tumors (1). Not only are the chromosomal aberrations nonrandom, some of them are also tumor type-specific.

Of the 2,700 solid tumors that have been cytogenetically characterized, bone and soft tissue tumors account for about 400 cases (2, updated). Specific rearrangements have been described for some of these neoplasms, for example, synovial sarcoma (3), Ewing's sarcoma (4), and myxoid liposarcoma (5, 6). In a subset of tumors, these abnormalities have been seen as the sole change; they are considered to be of pathogenetic importance, and are referred to as primary aberrations.

Neoplastic cells have increased genetic instability (7, 8), and thus a tendency to acquire additional chromosomal changes. These secondary aberrations may also be nonrandom, and they are thought to contribute to tumor progression. As a result, clonal evolution will take place within the tumor; cells with acquired changes that increase their proliferative capacity give rise to steadily expanding clones that eventually dominate the karyotype. It is of interest to investigate whether tumor areas with different morphologic features have different chromosome rearrangements, and thus to test the hypothesis that a relationship exists between the different histologic phases of tumor progression and the cytogenetic manifestations of clonal evolution. Mesenchymal tumors are often large, display both macroscopic and microscopic intratumor heterogeneity, and are suitable for such investigations.

Patient and methods

A 53-year-old, previously healthy, man had for 5 months noticed a painless, increasing swelling at the back of the right thigh. CT and MRI showed a 13-cm ovoid tumor between the hamstring muscles. The tumor was well demarcated and was composed of several nodules (Figure 1). A myxoid liposarcoma was diagnosed by fine-needle aspiration cytology. Chest radiographs were normal. The tumor was marginally excised. At the latest follow-up, 6 months postoperatively, there were no signs of local recurrence or metastasis.

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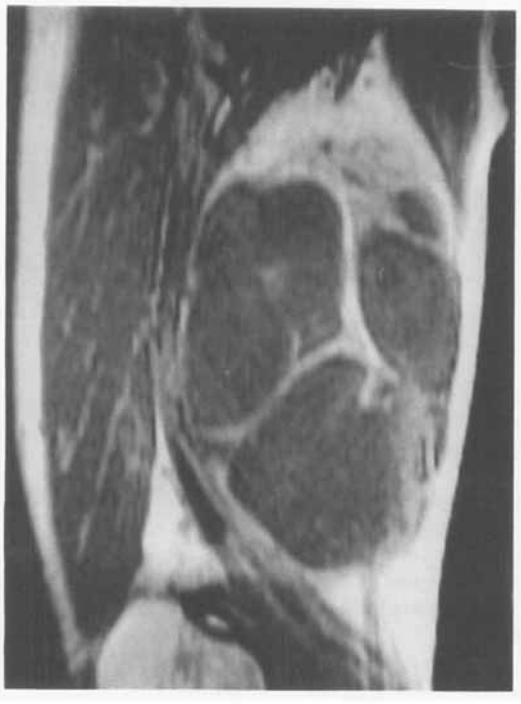

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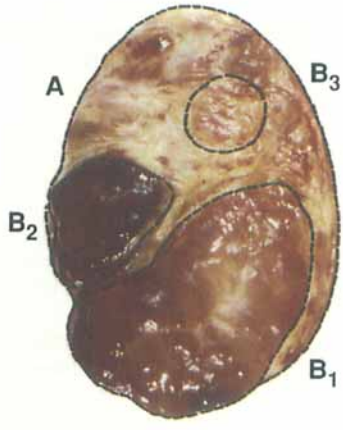

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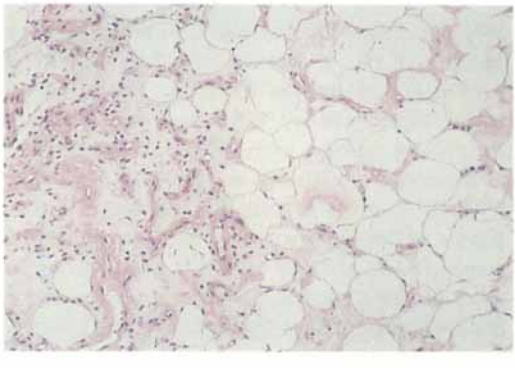

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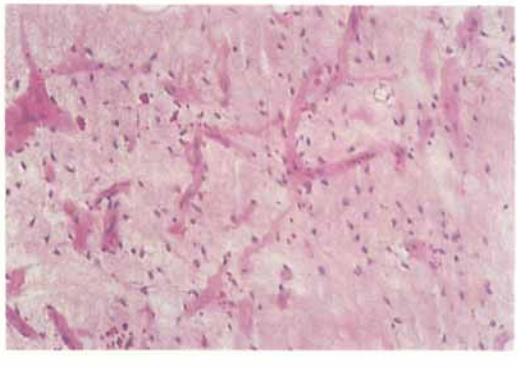

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Figure 1. A. Sagittal MR section through the lower right thigh demonstrating a lobulated soft tissue tumor in the posterior compartment.

B. Macroscopic picture of a cross section of the fresh tumor. The four areas from which the tissue samples were taken are marked.

C. Part of lipoma-like tissue from A, composed of large univacuolated fat cells with small, regular nuclei. To the left is a small, poorly delimited area of myxoid liposarcoma found. (HE, ×15)

D. Part of nodule B_1. Moderately cellular myxoid liposarcoma with abundant myxoid matrix. (HE, ×20)

Transection of the fresh specimen showed rather well-delimited nodules with myxoid, stringy, gelatinous surfaces. The nodules were completely encased in a lipoma-like tissue with a firm and faintly yellow surface. Samples were taken from the lipoma-like tissue (A) and from three nodules (B_1, B_2, B_3; Figure 1). Each of the four samples were divided into pieces for histopathologic and cytogenetic investigation.

Table 1. Results obtained from the four different parts of the liposarcoma

Sample	Histopathology	Karyotype	No. of metaphases	
			Abnormal	Normal
A	myxoid, partly lipoma-like	46,XY,t(12;16)(q13;p11)	69	0
B_1	myxoid	46,XY,t(12;16)(q13;p11)	36	0
B_2	myxoid	46,XY,t(12;16)(q13;p11)/46,XY, -16,+der(1)t(1;16)(p11;p11), t(12;16)(q13;p11)	68/12	2
B_3	myxoid	46,XY,-16,+der(1)t(1;12) (p11;q13),der(12)t(12;16)(q13;p11)	53	0

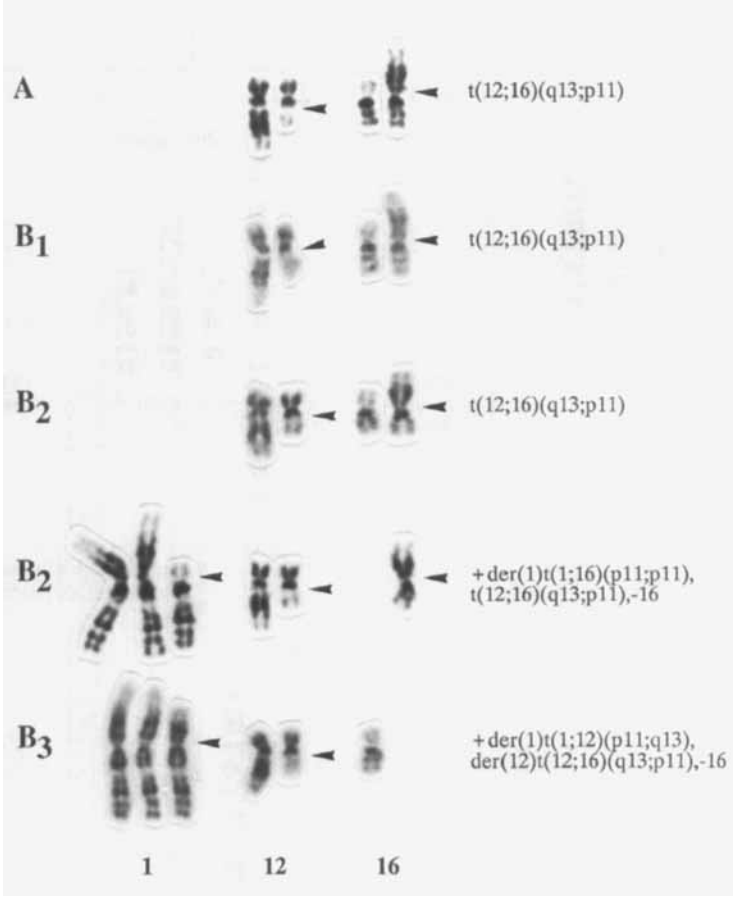

Figure 2. A. Partial karyotypes from the four samples. The normal homologues are shown to the left, arrowheads indicate breakpoints.

Histopathologic examination of the lipoma-like tissue (A) revealed ordinary-looking fatty tissue with small, poorly delimited areas of myxoid liposarcoma. Samples B_1, B_2, and B_3 showed the typical appearance of myxoid liposarcoma, with large pools of mucoid material (Figures 1C and D).

The tumor samples were cultured for 4–7 days and processed for chromosome analysis as described previously (9). The criteria for chromosome classification and for clonality were according to ISCN (10).

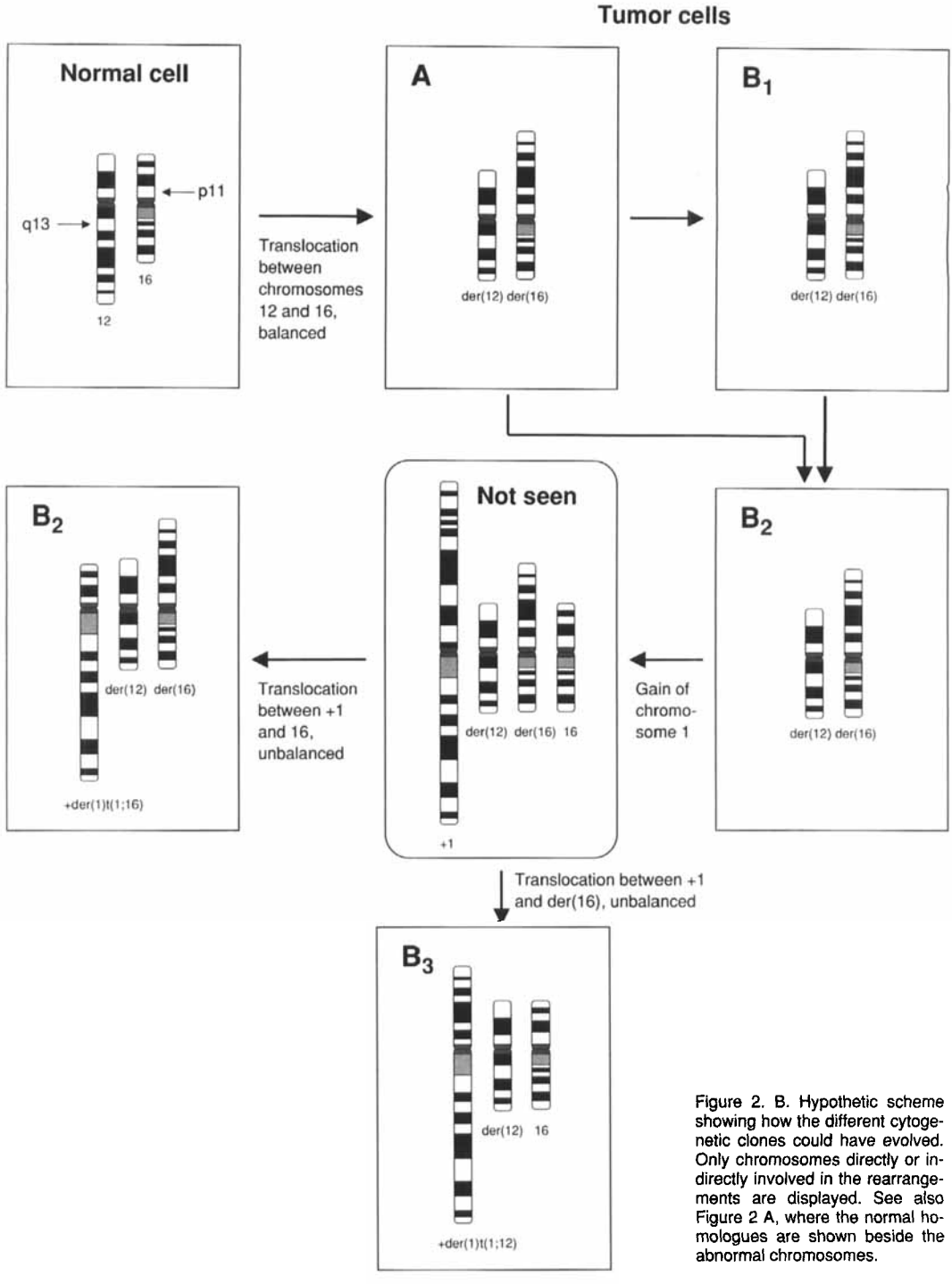

Figure 2. B. Hypothetic scheme showing how the different cytogenetic clones could have evolved. Only chromosomes directly or indirectly involved in the rearrangements are displayed. See also Figure 2 A, where the normal homologues are shown beside the abnormal chromosomes.

Table 2. Karyotypes of myxoid liposarcomas described in the literature

Case	Localization	Karyotype[a]	Reference no.
1	retroperitoneal	46,XX,**t(12;16)(q13;p11)**	5
2[c]	thigh	46,XY,**t(12;16)(q13.3;p11.2)**	6
3[c]	lower leg	46,XY,**t(12;16)(q13;p11)**	11
4	leg	46,XY,**t(12;16)(q13;p11)**	12
5[b]	thigh	46,XY,**t(12;16)(q13;p11)**	13
6	thigh	46,XX,t(3;15)(p23;q15),**t(12;16)(q13;p11)**	5
7	lower leg	46,XY,del(6)(q21),**t(12;16)(q13;p11)**	5
8	thigh	46,XX,**t(12;16)(q13;p11)**/46,XX,i(7q),**t(12;16)(q13;p11)**	6
9[c]	thigh	47,XY,+8,**t(12;16)(q13.3;p11.2)**	6
10	not given	47,X?,+8,+t(1;?)(p11 or p13;?),**t(12;16)(q13;p11)**	14
11	thigh	46,XY,**t(12;16)(q13;p11)**/46,XY,-16,+der(1)t(1;**12**)(p11;**q13**),der(12)**t(12;16)(q13;p11)**,/46,XY,-16,+der(1)t(1;16)(p11;**p11**),der(12)**t(12;16)(q13;p11)**	our case
12[b]	thigh	46,XY,+1,-16,der(1)t(1;**12;16**)(p11;**q13;p11**),der(12)t(1;**12;16**)(p11;**q13;p11**)	5
13	thigh	46,XY,-12,-16,+der(12)**t(12;16)(q13;p11)**,+der(16)t(12;**16**)(q22;**p11**)	6
14	thigh	47,XY,+8,t(1;**12**)(q42;**q13**),t(10;**16**)(q22;**p11**)/47,XY,+8	15
15	retroperitoneal	83,XY,del(1)(q11),del(2)(p11),del(3)(p21),6q+,11p+,t(**12**;19)(**q13**;p13 or q13),12p+	12
16	a. metastasis to abdominal wall	46,XY,t(11;**12**)(p15;**q13**)	15
	b. retroperitoneal metastasis	47,XY,-2,del(6)(q11),t(11;**12**)(p15;**q13**),der(15)t(15;?)(q24;?),der(21)t(1;21)(q12;q22),+2mar	
17	metastasis to lung	46,XY,t(12;**16**;16)(p11q21;**p11**;q12)	16
18	thigh	42-45,X,-Y,der(12)	17

[a] Rearrangements of 12q13 and 16p11 in bold type.
[b] With well-differentiated areas.
[c] Mixed (myxoid and round cell) liposarcoma.

Results

Clonal chromosome changes were found in all four tumor parts (Table 1, Figures 2A and B). In samples A and B_1, a reciprocal translocation between chromosomes 12 and 16, t(12;16)(q13;p11), was the sole aberration in all the cells.

Totally, 82 cells were analyzed from sample B_2, 68 of which had t(12;16)(q13;p11) as the sole abnormality. Another 12 cells had t(12;16) and an additional, unbalanced rearrangement. The short arm of the homologous chromosome 16 had been translocated onto the short arm of an extra chromosome 1, giving rise to a derivative (der) chromosome containing the centromere of chromosome 1. The remaining parts of chromosomes 1 and 16 had been lost. The mosaic karyotype was 46, XY, t(12;16)(q13;p11)/ 46, XY, –16, +der(1)t(1;16)(p11;p11), t(12;16)(q13;p11). Two cells with a normal male karyotype (46,XY) were also observed, confirming that the 12;16-translocation was not constitutional.

In sample B_3, all the analyzed cells had the derivative chromosome 12 resulting from the t(12;16). The part of the long arm of chromosome 12 that in samples A and B_1 was translocated to chromosome 16 had been translocated to the short arm of an additional chromosome 1. The remainder of the abnormal chromosome 16 was lost. The karyotype was 46, XY, –16, +der(1) t(1;12) (p11;q13), der(12) t(12;16) (q13;p11).

Discussion

A t(12;16)(q13;p11) has been consistently found in myxoid liposarcoma, but never in other tumors. Including our case, 18 cytogenetically abnormal myxoid liposarcomas, three of which were mixed (myxoid and round cell), have been reported (Table 2). The t(12;16)(q13;p11) was found in 11 tumors; in 5 tumors (Cases 1–5) as the sole aberration and in 6 tumors (Cases 6–11) together with additional changes. Three tumors (Cases 12–14) displayed variant translocations with both 12q13 and 16p11 involved, and three tumors had involvement of either 12q13 (Cases 15 and 16) or 16p11 (Case 17). In Case 18, only a der(12) without any specified breakpoint was found. Thus, chromosome 12 was rearranged in all

the tumors, with the breakpoint in 12q13 in all but two, and rearrangement of 16p11 was found in all but three tumors. The chromosome most frequently involved in additional changes in tumors with more complex aberrations (Cases 10–12 and 14–16) was chromosome 1. The chromosome 1 changes thus seem to be progression-related, secondary aberrations in myxoid liposarcomas, as they are in several other tumor types (1). Moreover, the unbalanced variant translocation t(1;12;16)(p11;q13; p11), which is similar to the rearrangement found in sample B_3, was also found in another tumor (Case 12).

The chromosome segment that includes the three bands 12q13–15 is involved in specific chromosome aberrations in three benign tumor types: pleomorphic adenoma of the salivary gland (18,19), uterine leiomyoma (20), and lipoma (9). In lipomas, t(3;12)(q27-28;q13-15) is the most common aberration, but recombinations of 12q13-15 with other bands are also frequent. In spite of this diversity, a t(12;16) has never been detected. This indicates that a change within 12q13-15 is of importance for the development of lipogenic tumors, but that malignant growth occurs only if 12q13-15 is recombined with 16p11. The fact that no lipoma with t(12;16) has been reported among the 150 cases investigated (2, updated) favors the assumption that the tumor reported here, in spite of the partly lipoma-like histology in sample A, was a de novo liposarcoma. This is also in agreement with the notion that liposarcomas develop from primitive mesenchymal cells and not from preexisting lipomas (21).

We found karyotypic variation within the tumor. The variant translocations in samples B_2 and B_3 had evidently arisen in cells carrying a t(12;16)(q13;p11) and thus signify clonal evolution (Figure 2B). The fact that t(12;16)(q13;p11) was found as the sole change in all the cells from samples A and B_1, and in the majority of the cells from sample B_2, shows that this was the primary aberration. At least one cell must later have acquired an extra copy of chromosome 1, which then lost most of the short arm. It is not possible to know whether this loss occurred prior to or at the time when chromosome 1 underwent translocation, because no cell from this intermediate stage was detected. In one subpopulation of cells from sample B_2, the short arm of the chromosome 16 not involved in the t(12;16) was translocated onto the short arm of the additional chromosome 1, and in all the cells from sample B_3, the part of the long arm of chromosome 12 that had originally been translocated to chromosome 16 was translocated to the short arm of the additional chromosome 1. It is reasonable to assume that the complex clones in B_2 and B_3 were derived from the same cell with trisomy 1. This cell probably originated in B_2, because cells with only t(12;16) and cells with additional changes coexisted in that nodule. Descendants of cells with extra chromosome 1 material could then, before or after the 1;12-translocation took place, have initiated nodule B_3. It is also possible that the two clones with complex aberrations could have originated independently from two cells that both had acquired an extra chromosome 1. However, this would involve a more complicated evolutionary scheme and therefore seems less likely.

The different cytogenetic clones occurred in tumor parts with different macroscopic and microscopic appearances. Sample A, which contained only cells with t(12;16)(q13;p11), was taken from the lipoma-like tissue that surrounded the myxoid nodules. This macroscopic appearance, and the finding of more complex aberrations in B_2 and B_3, indicate that the nodules have developed from the lipoma-like tissue. Our case thus illustrates parallel tumor progression and cytogenetically detectable clonal evolution.

Acknowledgements

Supported by grants from the Swedish Cancer Society, the J A P Foundation for Medical Research, and the Lund University Medical Faculty.

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