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Correlation between Clinicopathological Features and Karyotype in Spindle Cell Sarcomas

A Report of 130 Cases from the CHAMP Study Group

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Soft-tissue tumors have proved to be a fruitful area for the identification of reproducible cytogenetic aberrations, especially among pediatric round-cell sarcomas and lipomatous tumors. Thus far, however, data regarding sarcomas of monomorphic spindle cell type have been limited and somewhat disappointing, with the notable exception of synovial sarcoma. As part of an ongoing international collaborative study, 130 karyotyped spindle-cell sarcomas were reviewed and classified histologically, without knowledge of the clinical and karyotypic data, with the aim of identifying objective correlations between morphology, karyotype, and clinical parameters. Clonal chromosomal abnormalities were identified in 82 cases studied (63%), but only in the group of synovial sarcomas was there clear correlation between the cytogenetic findings, in the form of a consistent t(X;18)(p11;q11), and morphology. Among leiomyosarcomas (41 cases) and malignant peripheral nerve sheath tumors (MPNSTs; 27 cases) as well as in individual examples of rarer entities, there was a general tendency for karyotypic complexity associated with frequent loss or rearrangement of chromosome arms 1p, 10p, 11q, 12q, 17p, and 22q. Rearrangements of 17q (the region of the *NF1* gene) were seen in 9/27 (33%) of MPNSTs. Among nine cases of solitary fibrous tumor (in which previous cytogenetic data are very limited) no consistent aberrations were identified. We conclude that, with the exception of synovial sarcoma, most spindle-cell sarcomas share with pleomorphic sarcomas the tendency for karyotypic complexity. There was no indication (in most of these lesions) that detectable cytogenetic aberrations could either facilitate their diagnosis or help to determine prognosis. There is a clear need to further study and understand the significance of multiple chromosomal abnormalities in this group of mesenchymal neoplasms with the particular goal of determining their role in the process of tumor development. *(Am J Pathol 1999, 154:1841–1847)*

Over the past 15 years it has increasingly been recognized that soft-tissue tumors, especially sarcomas, are very often characterized by reproducible chromosomal aberrations, many of which appear to be specific for a given tumor type. Common among these aberrations are reciprocal translocations, and the characterization of these translocation breakpoints has facilitated not only investigation of the molecular pathogenetic basis of these tumors but also, in concert with modern molecular techniques such as reverse transcription polymerase chain reaction and fluorescent *in situ* hybridization, has allowed development of novel diagnostic methods based on the detection of distinctive fusion gene products. In turn, the latter has enabled relatively objective genetic confirmation of diagnoses using only tiny biopsies or fine needle aspiration specimens, albeit occasional doubts have been raised regarding the specificity of some breakpoints. As has been the case with leukemias and lymphomas (and in stark contrast to most epithelial malignancies, with the exception of renal and thyroid tumors), cytogenetic analysis has been playing an appreciable role in both the basic and clinical investigation of soft-tissue neoplasms,[1,2] and the recent suggestion that typing of fusion genes may have prognostic significance[3,4] has further enhanced this role.

As a reflection of the potential importance of the clinical application of cytogenetics to soft-tissue tumors, an

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international collaborative group (the CHAMP study group) comprising cytogeneticists, pathologists, and surgeons was established in 1993 (and first met in 1994) to correlate chromosomal analysis and morphology in these lesions. Although the relevance of karyotypic analysis has now been well established in small-round-cell neoplasms and in lipomatous tumors,[1,2,5,] it has been the group's goal to study as large a spectrum as possible of connective tissue neoplasia, subject to the availability of an adequate number of karyotyped specimens. Work done in 1996 on the family of pleomorphic (malignant fibrous histiocytoma (MFH)-like) sarcomas revealed little in the way of meaningful diagnostic or prognostic correlations, mainly due to the extreme complexity of the karyotypes in these lesions.[6] It was then decided to move on to analyze the group of spindle-cell sarcomas arising in soft tissue, and it is these lesions that are the focus of the present report.

Materials and Methods

A group of 136 spindle-cell sarcomas arising in soft tissue that had been karyotyped successfully in Lund and Leuven between 1984 and 1996 were selected for study based on the following criteria: 1) tumors originally diagnosed as leiomyosarcoma, malignant peripheral nerve sheath tumor (MPNST), synovial sarcoma, fibrosarcoma, hemangiopericytoma, and solitary fibrous tumor were included; 2) tumors originating from visceral organs (eg, gastrointestinal tract and uterus) or bone were excluded; 3) tumors classified as dermatofibrosarcoma protuberans (DFSP) and desmoid fibromatosis were excluded because of their greater tendency to show morphological overlap with benign lesions and their minimal or absent metastatic potential (these lesions will form part of a separate future CHAMP study).

For cytogenetic analysis, fresh tumor specimens in all cases were disaggregated with collagenase, cultured (for less than 10 days), harvested, and stained as previously described.[7] Chromosomal aberrations and karyotypes were described according to the International System for Human Cytogenetic Nomenclature.[8] In light of the complexity of many of the karyotypes and after initial appraisal of the results (as well as data in the literature), the chromosome aberrations identified were broken down into the following subgroups: t(X;18)(p11;q11), rearrangements of 12q (distinguishing as an important subset those with 12q13–15 aberrations), ring chromosomes, homogeneously staining regions/double minute chromosomes (hsr/dmin), trisomy 7, deletion or rearrangement of the following: 1p, 4q, 6q, 9p, 10p, 11p, 11q, 12p, 17p, 22q, Xp, Xq, aberrations other than those listed above (other), and normal karyotype (N).

For histopathological analysis, all of the paraffin blocks in each of the 136 cases were recut and re-examined by three of the group members (C.D.M. Fletcher, J. Rosai, and G. Tallini) without any knowledge of the clinical or karyotypic data or of the previous (original) diagnosis. Immunohistochemical analysis, using conventional markers of differentiation routinely used in the diagnosis of soft-tissue neoplasms, was performed in almost all of the cases. When available, electron microscopic materials were reappraised at the time of group review. The tumors were then classified according to the following morphological criteria.

Leiomyosarcoma was characterized by the presence of eosinophilic spindle cells with blunt-ended, cigar-shaped nuclei arranged mainly in a fascicular pattern, with fascicles often intersecting at 90° angles. More pleomorphic examples of this tumor type had been included in a previous CHAMP study and were not reanalyzed here. Immunohistochemically, tumors with these morphological features were required to show extensive positivity for smooth muscle actin (SMA); desmin was also strongly, if only focally, positive in most cases.

Malignant peripheral nerve sheath tumor (MPNST) was characterized usually by the presence of pale spindle cells with indistinct cytoplasmic margins and wavy, tapering, or S-shaped nuclei, often arranged in fascicles with alternating cellular and more myxoid areas and with a frequent tendency to show perivascular accentuation. Tumors with these suggestive features were also required to show either S-100 protein immunopositivity (in the absence of epithelial membrane antigen or keratin reactivity), clear evidence of origin from a nerve or neurofibroma, or ultrastructural evidence of Schwann cell differentiation or else to occur in a patient with well documented neurofibromatosis type I (von Recklinghausen's disease).

Synovial sarcoma was subclassified into three groups: monophasic (spindle cell), biphasic, and poorly differentiated. Biphasic lesions were characterized by the classical admixture of basophilic spindle cell fascicles and glandular or epithelial-lined structures; monophasic lesions, in addition to a basophilic fascicular appearance, commonly showed wiry stromal collagen and focal hyalinization. All three subtypes were often associated with a pericytoma-like branching vascular pattern, focal calcification, and stromal mast cells. Immunohistochemically, all cases were required to show convincing positivity for epithelial membrane antigen and/or keratin in the spindle or poorly differentiated cells, aside from any positivity in glandular structures. Staining for desmin was by definition absent, and any positivity for actin should only be focal.

Solitary fibrous tumor was characterized by fairly uniform pale spindle cell morphology with ovoid or tapering, often vesicular nuclei, a patternless (or very focally fascicular) architecture, marked variation in cellularity with frequent areas of stromal hyalinization, the common presence of a branching pericytoma-like vasculature, and immunopositivity for CD34 in the absence of reactivity for epithelial membrane antigen, keratin, S-100 protein, and desmin.

Miscellaneous

This category included examples of 1) myofibroblastic sarcoma, being spindle-cell sarcomas reminiscent of leiomyosarcoma except for their paler cytoplasm and more pointed or tapering nuclei, 2) mesenchymal chon-

Table 1. Histological Classification of 130 Spindle-Cell Sarcomas Studied

	n
Leiomyosarcoma	41
Malignant peripheral nerve sheath tumor (MPNST)	27
Synovial sarcoma	
Biphasic	5
Monophasic	29
Poorly differentiated	8
Solitary fibrous tumor	9
Miscellaneous	
Myofibroblastic sarcoma	3
Hemangiopericytoma	1
Mesenchymal chondrosarcoma	1
Inflammatory myofibroblastic tumor	1
Infantile fibrosarcoma	1
Leiomyo- or myofibro-sarcoma	1
Spindle-cell sarcoma NOS	3
Total	130

drosarcoma, bearing a close resemblance to so-called hemangiopericytoma except for the presence of cartilaginous nodules, 3) inflammatory myofibroblastic tumor/inflammatory fibrosarcoma, being composed of fibroblastic/myofibroblastic fascicles with minimal to mild nuclear atypia and a prominent lymphoplasmacytic infiltrate in the stroma, 4) hemangiopericytoma, being tumors composed of close-packed uniform short spindle cells associated with numerous thin-walled, variably dilated branching vessels and without any immunohistochemical evidence of specific differentiation, 5) infantile fibrosarcoma, being a fascicular spindle-cell sarcoma with a herringbone architecture, palely eosinophilic cytoplasm, tapering nuclei, and no immunohistochemical evidence of specific differentiation, and 6) unclassified spindle-cell sarcomas, being lesions that lacked either distinctive architectural or immunophenotypic features.

Results

Among the 136 tumors included initially, 6 were excluded after review for the following reasons: 3 were benign nerve sheath tumors and 1 each was a benign fibrous histiocytoma, an unclassified benign fibrous neoplasm and a fibrosarcomatous (higher grade) example of DFSP. This left 130 tumors available for detailed analysis. Their breakdown by histological type is shown in Table 1. Overall, 82 of 130 cases (63%) showed clonal karyotypic abnormalities. Among the cases studied, only 7 (5 leiomyosarcomas, 1 MPNST, and 1 synovial sarcoma) showed homogeneously staining regions or double minute chromosomes. Correlation between histological diagnosis and the most frequent karyotypic aberrations is shown in Table 2.

Leiomyosarcoma

Forty-one cases were classified histologically as leiomyosarcoma. Patient age ranged from 2 to 86 years; 31 patients were aged 50 or more. Twenty-one patients were male and twenty were female. Anatomical distribution was as follows: limbs and limb girdles, 24 cases; trunk, 4 cases; abdomen/retroperitoneum, 9 cases; and other, 4 cases. Among the limb and truncal lesions, 7 were subcutaneous and 17 were subfascial. Thirty-two cases were high grade, 8 were intermediate, and 1 was low grade.

Twenty-four cases (58.5%) had a normal karyotype, most likely representing overgrowth of non-neoplastic stromal cells in tissue culture. One case showed loss of the Y chromosome as a sole anomaly. Sixteen cases (39%) showed complex karyotypes with multiple clonal abnormalities, among which the most frequent were loss or rearrangement of 12q (nine cases, three involving 12q13–15), loss of 1p (eight cases), loss of 11q or 10p (six cases each), and loss of 6q, 11p, or 22q (four cases each). Three cases each showed either deletion or rearrangement of 17p or a ring chromosome. All sixteen cases showed a variety of other less frequent aberrations affecting multiple different chromosomes. There were no recognizable differences in terms of anatomical location, depth, grade, development of metastases, or tumor-related death between tumors having a normal or abnormal karyotype, nor did any of the clonal aberrations detected show any evident association with any of these clinical parameters.

Table 2. Correlation of Histological Type with Karyotypic Aberrations in 130 Spindle-Cell Sarcomas Studied

	Total cases	t(X;18)	Ring	1p	6q	9p	10p	11p	11q	12q	17p	17q	22q	Other	N
Leiomyosarcoma	41		3	8	4	2	6	3	6	9	3		4	18	24
MPNST	27		7	8	6	8	9	7	9	3	8	9	8	19	7
Synovial sarcoma	42	26	1	2			1	1	1	1	2			5	11
Solitary fibrous tumor	9									1	1			6	2
Myofibroblastic sarcoma	3													2	1
Hemangiopericytoma	1													1	
Mesenchymal chondrosarcoma	1									1				1	
Inflammatory myofibroblastic tumor	1														1
Infantile fibrosarcoma	1													1	
Myosarcoma NOS	1													1	
Spindle-cell sarcoma NOS	3													1	2
Total	130	26	11	18	10	10	16	11	16	15	14	9	12	55	48

Note that many individual tumors showed multiple aberrations.

Table 3. Cytogenetic Findings in Nine Cases of Solitary Fibrous Tumor

Case ref	Karyotype
Lu 265	77, XXY, +Y, +3, +8, +10, +12, +14, +17, +21/78, idem, +19/46, XY
Lu 315*	46, XY
Lu 318	72, X, −X, del(1)(q21), add(7)(p22), inc/46, XX
Lu 319	46, XY, t(2;17)(p16;q11), ins(7;11)(q36;q14q23)/46, XY
Lu 321	46, XX, tas(14;19)(p13;q13)/46, XX
Lu 316*	46, XY, t(6;12;19)(p22;q13;p13)/47, idem, +5/46, XY
Le 205†	43–46, XY, add(17)(p11)
Le 209	47, XX, +21
Le 226	46, XY

*Published as hemangiopericytoma in Ref. 23.
†Published in Ref. 22.

Malignant Peripheral Nerve Sheath Tumor

Twenty-seven cases were classified histologically as MPNST. Patient age ranged from 10 to 74 years, and the age distribution was evenly spread. Sixteen patients were male and ten were female; seven patients had von Recklinghausen's disease. Anatomical distribution was as follows: limbs and limb girdles, 16 cases; trunk, 4 cases; retroperitoneum, 4 cases; and other, 3 cases. Among the limb and truncal lesions, one tumor was subcutaneous and the other 18 were subfascial. Sixteen cases were high grade, nine were intermediate, and two were low grade. Two tumors arose in a pre-existing neurofibroma, and three tumors showed evidence of heterologous differentiation.

Seven cases (26%) had a normal karyotype. Twenty cases (74%) showed clonal aberrations, most often with a complex karyotype. The most frequent abnormalities were loss or rearrangement of 10p, 11q, or 17q (nine cases each) and loss or rearrangement of 1p, 9p, 17p, or 22q (eight cases each). Seven cases each showed a ring chromosome, trisomy 7, or rearrangement of 11p. Only two cases showed rearrangement of 12q13–15. Eighteen cases showed a variety of other less frequent aberrations affecting multiple different chromosomes. Complex rearrangements were more common in patients with von Recklinghausen's disease or in tumors showing heterologous differentiation. Among the cases with 17q rearrangements, three of nine had von Recklinghausen's disease. There were no evident correlations between karyotypic abnormality and any clinical parameter in these patients.

Synovial Sarcoma

Forty-two cases were classified histologically as synovial sarcoma. Patient age ranged from 11 to 82 years; 31 patients were aged 50 or under. The sex incidence was equal. Anatomical distribution was as follows: lower limb and limb girdle, 23 cases; upper limb and limb girdle, 7 cases; trunk, 4 cases; and other, 7 cases. In one case the location was unknown. Among the limb and truncal lesions, 2 cases were subcutaneous and 32 were subfascial. Twenty-nine cases were monophasic (spindle cell), eight were poorly differentiated, and five were biphasic. Twenty-seven tumors were high grade and fifteen were intermediate grade.

Eleven tumors (26%) had a normal karyotype. Thirty-one cases (74%) showed clonal abnormalities, most of which were relatively simple. Twenty-six cases (84% of those with an abnormal karyotype) showed a t(X;18)(p11;q11); in twenty-two of these, this translocation was combined with a variety of other infrequent clonal aberrations, among which were rearrangements of 11q (seven cases), 22q (five cases), and 11p (four cases). Three cases each showed rearrangements of 12q, 17p, or Xp or a ring chromosome. Four cases showed clonal abnormalities in the absence of either a classical t(X;18) or complex variant translocations involving chromosomes X and 18. One case showed a simple Xq rearrangement, two showed multiple chromosome rearrangements (one being very complex), and one showed multiple trisomies. There was no evident correlation between karyotype and either histological subtype or any recorded clinical parameter. In particular, there were no clinicopathological differences between those cases having or not having an X;18 translocation.

Solitary Fibrous Tumor

Nine cases were classified histologically as solitary fibrous tumor. Patient age ranged from 46 to 85 years (median, 53); there were six males and three females. Anatomical distribution was as follows: limbs and limb girdles, 5 cases; abdomen/retroperitoneum, 2 cases; and 1 case each in the pleura and oral cavity. Among the limb and limb girdle lesions, one was subcutaneous and the other four were subfascial. Unusually (and most likely reflecting the sarcoma interest of the institutions concerned), six of the nine cases showed histological features (mitoses $>$ 4 per 10 high-power fields, necrosis) of malignancy.[9]

Two cases had a normal karyotype and seven showed clonal aberrations. The cytogenetic abnormalities identified were different in every case, and the results are detailed in Table 3. The only possible similarities detected were involvement of the pericentromeric region of chromosome 17 in two cases and gain of chromosomes 21 in two other cases. There were no evident correlations between karyotype and histology, anatomical location, or clinical outcome. In fact, the tumor with the most complex karyotype (ref Lu 265) appeared histologically benign and has shown no evidence of recurrence at 6 years follow-up.

Table 4. Miscellaneous Tumors

Case ref	Diagnosis	Karyotype
Lu 287*	Myofibroblastic sarcoma	45, XX, del(1)(p13), add(5)(p15), +8, der(9)t(9;12)(p11;p11), der(10;12)(q10;q10), −13, −15, del(15)(q15), −21, +2mar/44, idem, −9
Le 165	Myofibroblastic sarcoma	46, X, der(X)t(X;?22)(p22;q11), t(2;14)(q31;q23), −6, del(15)(q21), der(19)t(11;19)(q13;q13), −22, +2mar
Le 210	Myofibroblastic sarcoma	46, XY
Lu 330	Meningeal hemangiopericytoma	47, XX, +5
Lu 259	Mesenchymal chondrosarcoma	45, XX, der(4)t(4;12)(q35;q13), add(5)(p15), −8, −12, der(20)t(8;20)(q13;p13)/46, XX
Lu 320	Inflammatory myofibroblastic tumor	46, XY
Le 166†	Infantile fibrosarcoma	48, X, −X, +11, +11, +17/49, idem, +20/46, XX
Le 136	Myosarcoma NOS	82–87, XX, −X, −X, der(1)add(1)(p11)add(1)(q21), der(2)t(1;2)(p22;q33), add(6)(q15), add(7)(q11), add(19)(q13), dmin, inc/46, XX
Le 206	Spindle-cell sarcoma NOS	46, XY
Le 217	Spindle-cell sarcoma NOS	48–50, XY, +X, add(1)(q44), +add(4)(q35), add(6)(q27), +7, del(12)(q11), −13, −14, +20, +mar
Lu 282	Spindle-cell sarcoma NOS	46, XX

*Published as fibrosarcoma in Ref. 27, corresponding to sample I, piece A. The change in the description of the rearrangement involving chromosomes 10 and 12 is basically technical (due to the new possibilities given in the new nomenclature system ISCN (1995)).
†Published in Ref. 25.

Miscellaneous Tumors

Eleven cases fell outside the four categories detailed above, and the karyotypes are detailed in Table 4. Three were classified histologically as myofibroblastic sarcoma, of which two were examples of the recently described low-grade type[10] and one was high grade. All three arose in adults (two females and one male); two were located on the trunk and one on the neck. One showed a normal karyotype, the high-grade lesion (ref Lu 287) showed an exceedingly complex karyotype, including rearrangements of 1p, 9p, and 10p, and the remaining low-grade lesion (ref Lu 165) showed unbalanced aberrations, including changes in Xp and 11q. Both cases had similar deletions of 15q. There was one case of meningeal hemangiopericytoma with lung metastasis, which showed trisomy 5 as the sole clonal rearrangement. There was one extraskeletal mesenchymal chondrosarcoma of the lower limb in an adult female, which showed rearrangements of 12q13–15 and 4q as well as a variety of other rearrangements. There was one inflammatory myofibroblastic tumor in the abdomen of a 5-year-old boy, the karyotype of which was normal. There was one infantile fibrosarcoma in the leg of a 5-month-old girl, which showed characteristic gain of chromosomes 11, 17, and 20. There was one case in which the study group pathologists could not decide between leiomyosarcoma and myofibroblastic sarcoma (myosarcoma NOS), occurring in the chest wall of a 67-year-old female, which showed a complex karyotype with numerous rearrangements. There were three unclassified sarcomas, two of which showed a normal karyotype and one of which had a complex karyotype with multiple aberrations. Unfortunately, no ultrastructural data were available for these latter three cases.

Discussion

Although cytogenetic analysis has significantly transformed and expanded our understanding of the molecular pathogenesis (and our diagnostic options) in the small-round-cell and lipomatous subsets of soft-tissue neoplasms, its role or relevance in the areas of pleomorphic and more monomorphic spindle-cell sarcomas (which cumulatively represent the largest subsets of soft-tissue sarcoma in adults) has remained unclear. This largely reflects the relatively limited number of cases in these categories with well documented karyotypes as well as the evident heterogeneity in the cytogenetic aberrations identified.

With the notable exception of synovial sarcoma, in which more than 90% of the published cases have shown an X;18 translocation with or without additional aberrations,[11,12] other types of spindle-cell sarcoma have generally not been associated with any consistent or specific cytogenetic aberration. Because of this, interest instead has been focused on the frequency with which chromosomal regions harboring potentially relevant tumor suppressor genes (especially *TP53* on 17p and *NF1* on 17q) are involved in these tumor types.

Using data from the latest Catalog of Chromosome Aberrations in Cancer,[13] among the 51 leiomyosarcomas with previously published karyotypes (of which less than half were located in soft tissue rather than visceral locations), the most frequent rearrangements in soft-tissue examples (almost always in the setting of a complex karyotype) involved bands 1p36, 14p11, 19q13, 20q13, and 22q13. In addition, trisomy 7 and losses (monosomy) of chromosomes 4, 13, 14, 18, and 22 seem common. Our own data certainly support a central role for deletion of the chromosome arm 1p in these lesions,[14,15] although given the usual complexity of the karyotypes in this tumor type, it is impossible to determine whether a given aberration is a primary nonrandom event or else a secondary (or unrelated) event of unknown (or dubious) significance, at least in terms of tumor specificity. The involvement of 12q in nine cases (of which three showed 12q13–15 rearrangements) suggests at least some pathogenetic similarity with uterine benign smooth muscle tumors in which up to 50% have 12q13–15 rearrangements.[16,17] In future studies, it would be of interest to compare the karyotype of those gastrointestinal stromal

tumors that show smooth muscle differentiation with that of leiomyosarcomas at other sites.

As with leiomyosarcomas, the karyotypes of the less than 50 published examples of MPNST have generally been both very variable and complex.[18–20] The most frequently rearranged chromosome bands have been 7p22, 17p11 (the location of the *TP53* gene), 17q11 (the location of the *NF1* gene), and 22q11 (the location of the *NF2* gene). Among the numerical aberrations identified, commonest have been trisomy 7 and losses of X, 10, 16, 17, 18, 19, and 22. Our own data have served to further implicate chromosome regions 17q, 17p, 10p, and 22q and have drawn attention to a potential role for 1p and 11q. In fact, the relative frequency of 1p rearrangement in both leiomyosarcomas and MPNSTs adds weight to the hypothetical presence of one or more tumor-suppressor genes or else an (activated) proto-oncogene in that location. Our data further confirm the relatively frequent involvement of 17q and 22q (and hence the possible involvement of the *NF1* or *NF2* genes) in sporadic cases of MPNST unassociated with neurofibromatosis.

As far as synovial sarcomas are concerned, we were not able to add much to the existing literature as there are almost 100 previously published cases with abnormal karyotypes of which 84% have shown a t(X;18)(p11;q11) in 21% as the sole anomaly.[13] We too found that most of our cases showed additional aberrations (albeit much less complex than those in leiomyosarcoma or MPNST) but without significant predilection for any particular chromosomal region. Previous data[13,21] (which included six tumors from the present series[21]) have suggested gains of chromosomes 7, 8, and 12 and structural rearrangements of 3p21, 5q11, 19q13, and 22p11 as the commonest secondary aberrations, but our series may be too small to validate this. Among the four cases in our series with aberrations other than t(X;18), one showed involvement of Xp in alternative rearrangements. Our data confirmed previous evidence that there were no discernible differences (at the chromosomal level) between the three morphological subsets of synovial sarcoma. However, it is our intention now to further study the entire series (including those with a seemingly normal karyotype) using reverse transcription polymerase chain reaction to determine what proportion of the cases as a whole had molecular evidence of a t(X;18) and, at the same time, to see whether recently presented data concerning the correlations between the chromosomal breakpoint or fusion gene (ie, *SYT-SSX1* or *SYT-SSX2*) with both morphology and clinical outcome[3] can be reproduced.

Concerning solitary fibrous tumor, there are few published data regarding its karyotype,[22] the principal reason for which is likely reflected in the fact that this diagnosis has gained popularity (at extrapleural locations) only in the past few years. Before that time, most such cases were subsumed principally in the category of hemangiopericytoma, an entity that is hard to define and that is regarded by some as a pattern shared by a very heterogeneous and broad group of neoplasms. Published cytogenetic data concerning hemangiopericytoma includes less than 20 cases,[13] but among these, the most frequent rearrangements have involved 12q13–15 (50% of cases) and 3p12–21 (37% of cases). In the present study, seven tumors had originally been classified (before the study review) as hemangiopericytoma, and two of these had been published previously.[23] Among these seven, five were reclassified as examples of solitary fibrous tumor, one was reclassified as inflammatory myofibroblastic tumor, and one was reclassified as a cellular benign fibrous histiocytoma (and excluded from this analysis).

Among the nine cases diagnosed as solitary fibrous tumor in the present study, there were no consistent cytogenetic abnormalities, although it was notable that the karyotypes were all relatively simple when compared with those of leiomyosarcoma or MPNST. Only one case (from the leg of an adult male) showed a 12q rearrangement. Whether this failure to find any reproducible or distinctive chromosomal aberration in these lesions reflects reality or whether it might be due either to the fact that six of nine lesions (unusually) were histologically malignant or that the morphological pattern that we recognize as solitary fibrous tumor is a shared or nonspecific appearance can only be a matter of speculation at this time. Having said that, there is no logical basis on which to believe that malignancy would have diminished karyotypic consistency (especially in the setting of relatively simple karyotypes), and furthermore, we believe that the morphological criteria applied by the study pathologists when making this diagnosis were as strict as can reasonably be expected. Clearly, more karyotypic data on this tumor type need to be accumulated before any more concrete interpretation is possible.

From the cases in the miscellaneous category it is difficult to draw any significant conclusions. The one case of infantile fibrosarcoma showed the trisomies known to be customary in this tumor type.[24,25] No cases of adult fibrosarcoma were available for study, largely because this diagnosis is scarcely used nowadays (except for special morphological subsets, such as inflammatory fibrosarcoma and sclerosing epithelioid fibrosarcoma). The previously published karyotypic data on just six adult fibrosarcomas have revealed complexity with no reproducible abnormalities,[13,26,27] and the one case reported with an X;18 translocation[28] is now generally accepted to have been a monophasic synovial sarcoma. Among the other cases studied, the aberrations that we identified in one case each of meningeal hemangiopericytoma and mesenchymal chondrosarcoma showed no clear relationship to previously reported findings in these tumor types.

In conclusion, this karyotypic study of a large series of spindle-cell sarcomas, although confirming the reproducibility of the X;18 translocation in synovial sarcoma, has provided further substantial evidence that most other sarcomas of monomorphic spindle-cell type do not show tumor-specific chromosomal abnormalities comparable to the type seen in round-cell sarcomas, lipomatous tumors, and some myxoid neoplasms. Rather, they usually have complex karyotypes with multiple aberrations, and overall, this complexity does not correlate consistently with pathological or clinical parameters, such as histological grade or prognosis. The cytogenetic complexity of

these lesions essentially parallels that of their morphologically pleomorphic counterparts (the MFH-like group of tumors[6]); thus, the temptation to attribute the chromosomal anarchy seen in pleomorphic sarcomas to their relative lack of differentiation or their gross aneuploidy cannot be so easily sustained. Instead, it seems more likely that this subset of mesenchymal neoplasms has a different oncogenetic basis (or generic mechanism) that, rather than being predicated on a single (or primary and defining) genetic event, perhaps results from the progressive accumulation of multiple genetic hits in the manner now believed to operate for most epithelial malignancies. However, even that parallel will be limited by the fact that dysplastic or preinvasive precursors are not known to exist among these mesenchymal neoplasms, and hence, hypotheses regarding the acquisition of mutations that correlate with tumor development will be more difficult to substantiate. Although the role of known tumor suppressor genes (such as *TP53*, *NF1*, and *NF2*) is well documented and recognized in many of these tumor types, the increasingly consistent evidence that an additional such gene is likely located on 1p[29,30] merits further investigation, especially as this chromosome arm seems to be rearranged in a wide variety of tumor types.

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