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Review

Chromosomal Aberrations in Soft Tissue Tumors

Relevance to Diagnosis, Classification, and Molecular Mechanisms

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In recent years, significant progress has been made in identifying characteristic chromosomal rearrangements associated with several solid tumor types, notably sarcomas, a relatively rare subset of human cancer. Most sarcomas analyzed have been found to be characterized by recurrent chromosome translocations that are specific to histological types. We have reviewed published reports of chromosomal aberrations in benign and malignant soft tissue tumors and found an incidence of specific translocations in these neoplasms that ranged from 20% to 93% within histological tumor types. Identification of recurrent chromosomal abnormalities in benign tumors has resulted in a reappraisal of the general concept that benign tumors have a normal (diploid) chromosome constitution. The variety of recurrent changes present in the different tumor types attests to the cytogenetic diversity inherent in these tumors. The chromosomal rearrangements in each of the tumor types were unique and did not correspond to cancer-associated aberrations known from other solid or hematopoietic malignancies. Cytogenetics thus provides an essential adjunct to diagnostic surgical pathology in the case of malignant soft tissue tumors, which often present substantial diagnostic challenges. In addition, it represents another approach to determine the histogenetic origin of some tumors and identifies sites of gene deregulation for molecular analysis. Indeed, recent molecular analyses of several sarcoma-associated translocations have identified novel genes and novel mechanisms of their dysregulation. (Am J Pathol 1994, 144: 1121–1134)

Soft tissue tumors represent a heterogeneous group of neoplasms that exhibit differentiated features of various supporting tissues of the body. Together with tumors of the bone, they form a major histogenetic class distinct from neoplasms of epithelial, hematopoietic, or central neurogenic origin. The diagnosis of soft tissue tumors on occasion poses a considerable challenge to the pathologist and the clinician and necessitates the use of additional diagnostic techniques such as histochemical staining, electron microscopy, or immunohistochemistry.[1] Each of these techniques, however, has inherent limitations.

The identification of consistent chromosomal translocations associated with subtypes of leukemia or lymphoma over the past two decades has contributed to the transition of cancer cytogenetics from purely a research interest to a science which has become an integral part of the evaluation and diagnosis of human neoplasia.[2] It has also aided in directing therapy, determining prognosis, and identified sites of novel gene perturbation for molecular characterization. Cy-

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togenetic evaluation of tumors represents a relatively new and underutilized diagnostic approach in soft tissue tumors, although it has proven useful in relation to various poorly differentiated or undifferentiated sarcomas. We have reviewed the published literature on clonal chromosomal abnormalities in soft tissue tumors and identified several karyotypic aberrations that are specific to histological tumor types including some rare sarcomas.

Recent investigation of molecular alterations of genes at the sites of chromosomal alterations in sarcomas has led to the isolation of novel genes at translocation junctions and characterization of their mechanisms of deregulation. These studies are beginning to provide new insights into genetic mechanisms involved in sarcoma development and new diagnostic approaches for these tumors. Thus, utilization of cytogenetic and molecular genetic data in conjunction with histopathology as routine diagnostic techniques will ultimately provide a better clinical assessment of sarcomas similar to that available for leukemias and lymphomas.

Methods

The data for the present analysis were obtained by reviewing all published cases of clonal chromosomal aberrations in soft tissue tumors up to September 1993. The survey included more than 1500 cases published in over 50 different journals. Due to space considerations, only major review articles, books, key primary references, and the most recent references to original articles are cited in the text. The entire bibliography has been deposited with the editor of the *Journal* and will be made available to interested readers upon request. Complete clonal karyotypes, as defined by ISCN 1985[3] and 1991,[4] identified in direct or short term culture of primary, recurrent or metastatic tumors, before or after therapy, were included. Data from established cell lines and incomplete or partial karyotypes, or karyotypes reported in abstracts, were excluded. To be accepted as a specific aberration, a given abnormality had to be found as the sole anomaly in at least one tumor of a particular histopathological type and represent the most frequent aberration found in tumors of the same histopathological type.

The results of the analysis are summarized in Table 1. The recurrent abnormalities include complex translocations in which one or more additional variable chromosomes were involved in a specific translocation. In variant translocations, in which one of the recurrent translocation partners was replaced by a variable chromosome, only the breakpoint on the recurrently rearranged chromosome was considered. A majority of the specific abnormalities were part of complex karyotypes reflecting secondary changes acquired during tumor progression, some of which were also recurrent. Such nonrandom additional abnormalities have also been included in the analysis. Breakpoints that were nonrandomly involved in diverse rearrangements were also computed and their percentages calculated.

Diagnostic Chromosomal Rearrangements in Sarcomas

Synovial Sarcoma

Synovial sarcoma (SS) is a well defined clinical and morphological entity that occurs more commonly in adolescents and young adults, usually in the extremities in the vicinity of joints, most commonly the knee and lower thigh region. There are two distinct histological types of SS; the classical biphasic type with distinct epithelial and spindle cell components, and the monophasic type in which either the epithelial or the spindle cells predominate. Up to 20% of cases may be poorly differentiated, lacking clear epithelial or spindle cell elements. Separation of these tumors from other poorly differentiated sarcomas may be extremely difficult by conventional histopathology.[1]

Our analysis identified a total of 42 specimens with karyotypes described.[5–8] A specific t(X;18)(p11.2;q11.2) translocation was present in 38 tumors (90%) regardless of histological subtype, including in 8 cases as the sole abnormality. Complex translocations involving an additional chromosome were present in 7 other tumors (including 5 in which it was the only change). The translocation partners in these cases were chromosome 15 in 3 cases, and chromosomes 1 and 21 in 2 cases each. The recurrent and metastatic tumors typically had more additional or complex alterations than the primary tumor. Only 4 cases of SS without a t(X;18), including a case in which 2 metastases were removed one year apart, were reported[5]; however, in one case, a variant translocation involved chromosome 18 at band q11.2.

Only 2 tumors with a t(X;18)(p11.2;q11.2) and a diagnosis other than SS have been reported. One tumor was diagnosed as a fibrosarcoma[9] and the other as malignant fibrous histiocytoma (MFH).[10] Since the distinction between SS and other poorly differentiated sarcomas, including fibrosarcoma and MFH may be difficult, these tumors possibly represent histological variants of SS.

t(X;18)(p11.2;q11.2) thus appears to represent a very characteristic feature of SS. A number of studies

Table 1. *Recurrent Chromosomal Abnormalities in Soft Tissue Tumors*

Tumor Type*	Histology	No. Tumors† Analyzed	Recurrent Abnormalities‡	%§	Most Frequent Break-points¶	%
Benign mesenchymal neoplasms						
Lipoma	Typical	104	t(3;12)(q27-28;q13-14)	12	12q13-15	29
	Fibrolipoma		t/ins(1;12)(p32-34;q13-15)	7	6p21-23	9
	Angiolipoma		t/ins(12;21)(q13-15;q21-22)	6	11q13	5
	Myolipoma		t(2;12)(p21-23;q13-14)	5	1p36	5
	Myxolipoma		del(13)(q12q22)	11	13q12	4
			r	7		
Uterine leiomyoma		201	del(7)(q11.2-22q31-32)	35	12q13-15	10
			t(12;14)(q14-15;q23-24)	13	14q22-24	5
			t(12;14),−22	6	1p36	9
			+12	8	6p21	9
			r	7		
			del(13)(q12q33)	2		
Endometrial polyp		8	t(6;20)(p21;q13)	25	6p21	38
					12q13-15	38
Desmoid tumors		13	Telomeric fusion	38		
			del(5)(q13-31)	23		
Malignant mesenchymal neoplasms						
Synovial sarcoma	Monophasic Diphasic	42	t(X;18)(p11.2;q11.2)	90	18q11.2	2
Clear cell sarcoma		14	t(12;22)(q13-14;q12-13)	7		
			t(12;22),+8	57		
Liposarcoma	Myxoid	44	t(12;16)(q13;p11)	59	12q13	9
			t(12;16),+8	18	16p11	2
	Well differentiated	18	Near-diploid count, r, tas, hsr, large markers	100		
	Pleomorphic	13	Hyperdiploid count, poor morphology, multiple, complex non-recurrent aberrations	100		
Rhabdomyosarcoma	Alveolar	28	t(2;13)(q35-37;q14)	68	13q14	7
			t(1;13)(p36;q14)	14		
Leiomyosarcoma		42			1p13-36	36
					7p11-21	19
					1q32	12
					13q14	12
					14p11	12
Ewing's sarcoma		83	t(11;22)(q21-24;q11-13)	50	22q11-12	8
			t(11;22),+8	25		
			t(11;22),der(16)			
			t(1;16)(q11-25;q11.1-24)	11		
Chondrosarcoma	Extraskeletal myxoid	11	t(9;22)(q22;q11-12)	27		
Askin's tumor		8	t(11;22)(q24;q12)	50	22q11-12	25
			t(11;22),+8	25		
Peripheral neuroepithelioma		23	t(11;22)(q23-24;q11-12)	87	22q11.2-12	9
					11q23	4
Congenital fibrosarcoma		7	+11,+20	43		
			+11,+20,+17	43		
Malignant fibrous histiocytoma		32	tas, r, dic	59	19p13	31
			hsr, dmin	13	1q11	28
					11p11	22
					1p36	16
Intra-abdominal desmoplastic small round cell tumor		5	t(11;22)(p13;q11.2-12)	60	22q13	20
Endometrial stromal sarcoma		8	t(7;17)(p15-21;q11.2-21)	13	7p21	13
			t(7;17),del(11)(q13-21q21-23)	25	11q13	13
Hemangiopericytoma		10	t(12;19)(q13;q13.3)	20	19q13.3	30
					12q13-14	30
Malignant mesothelioma		85	del(3)(p13-23)	48	1p11-22	42
			del(9)(p12-22)	25	2p11-23	24
			del(6)(q11-25)	21	12q11-23	21
			−22	22		
			−18	12		

* Including primary, recurrent, and metastatic tumors.
† Only cases with clonal abnormality.
‡ Including complex translocations.
§ Percentage of tumors with specific abnormality in relation to number of tumors with clonal changes.
¶ Including variant translocations.

have documented the reliability of the presence of the t(X;18) in confirming a diagnosis of SS.[6,7,10,11]

Clear Cell sarcoma

Clear cell sarcoma (CCS) is a rare deep-seated malignant neoplasm of young adults usually associated with tendons and aponeuroses. A neural crest origin has been suggested, based on the demonstration of melanin, melanosomes, and premelanosomes in many cases.[1] Since approximately 50% of the tumors stain for melanin and ultrastructurally show premelanosomes, it has been suggested that the neoplasm be renamed "malignant melanoma of soft parts." Although the clinical course is slow, prognosis is poor.

The karyotypic findings confirm the observation that CCS is a distinct clinicopathological entity. Fourteen cases of CCS have been characterized cytogenetically to date and in 9 tumors (64%) a consistent t(12;22)(q13–14;q12–13) has been reported.[12] The translocation is unique to CCS and therefore distinguishes it from other tumor types, particularly metastatic cutaneous malignant melanoma—a very important clinical distinction. The translocation has been observed as the sole abnormality in one case as a separate clone. All the other cases contained multiple numerical and structural abnormalities. Trisomy or tetrasomy 8 was present as an additional nonrandom event in 57% of the cases.

The breakpoints of the t(12;22) have recently been characterized at the molecular level.[13] The *EWS* gene on 22q, originally cloned from the t(11;22) translocation of Ewing's sarcoma (see below), is rearranged with a transcription factor gene, *ATF1*, on chromosome 12. A fusion mRNA transcript is produced in which the RNA-binding domain of *EWS* is replaced by the DNA-binding domain of *ATF1*. The functional consequences of this translocation remain to be determined.

Liposarcoma

Liposarcoma (LPS) is one of the most common soft tissue sarcomas in adults. The tumor occurs most often in the extremities, particularly the thigh and retroperitoneum. It is remarkable for its frequent large size and the variable histological picture which closely correlates with clinical behavior. Four basic types are recognized: 1) myxoid, 2) round cell, 3) well differentiated, and 4) pleomorphic.[1] Cytogenetic reports of LPS are relatively few; only the myxoid subtype has been analyzed in sufficient numbers.

Myxoid LPS (M-LPS) is the most common variant and accounts for up to 50% of all LPS. Histologically, the tumor is composed of proliferating lipoblasts in varying stages of differentiation, a delicate plexiform capillary pattern, and a myxoid matrix. Multiple recurrences of the tumor are common, and the 5-year survival rate is more favorable than that of the round cell and pleomorphic types.[1]

The primary cytogenetic change in M-LPS is a highly consistent t(12;16)(q13;p11) noted in 34 of 44 tumors (77%) studied.[14–20] The translocation was present as the sole abnormality in 14 tumors. Trisomy 8 has been observed in 18% of the tumors as an additional nonrandom abnormality. Complex translocations were noted in 2 cases. Variant rearrangements involved band 12q13 only in 4 tumors and 16p11 in one case. One other case showed involvement of both 12q13 and 16p11 in separate rearrangements. The breakpoints of t(12;16) have been mapped to 12q13.3 and 16p11.2. The specificity of the t(12;16) in M-LPS is helpful in distinguishing M-LPS from other classes of myxoid tumors. Also, in its less differentiated forms, M-LPS may mimic other forms of sarcomas and, in some of these tumors, reliable diagnosis may not be possible in the absence of lipoblasts. In such instances the finding of a t(12;16) has diagnostic value.

Two groups have independently cloned the translocation breakpoints of the t(12;16).[21,22] The breakpoint on chromosome 12 involves the transcription factor gene *CHOP*, a member of the CCAAT/enhancer binding protein family, which may be involved in adipocyte differentiation. The *CHOP* gene, which has a DNA-binding domain and is a transcriptional activator, is rearranged with a gene on chromosome 16 designated *TLS* or *FUS*, which has an RNA-binding domain. The *CHOP* rearrangement appears specific for M-LPS. Other tumors with cytogenetic rearrangements of 12q13–15 such as lipoma, uterine leiomyoma, pleomorphic salivary gland adenoma, CCS, and hemangiopericytoma do not show rearrangement within the *CHOP* gene.[17,23]

Well differentiated liposarcomas (WD-LPS) usually simulate lipomas closely. WD-LPS have a tendency to recur locally, and distant metastases are rare.[1] Cytogenetically, all WD-LPS are characterized by telomeric associations, ring chromosomes, and giant marker chromosomes which may contain homogeneously staining regions (hsr).[16] The tumors are usually near-diploid with good chromosome morphology. A similar cytogenetic picture has been observed in atypical lipomas and some MFH.[24,25]

Pleomorphic liposarcomas (P-LPS) are highly metastatic, have a disorderly growth pattern, and show an extreme degree of cellular pleomorphism including bizarre giant cells.[1] The cytogenetic pattern is different from that of WD-LPS. The chromosome numbers are higher and extensive numerical and structural rearrangements (including numerous unidentifiable marker chromosomes) are displayed. No consistent abnormalities specific to P-LPS were observed. The cytogenetic pattern may reflect the advanced or highly aggressive nature of this malignant lesion.[16]

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma affecting individuals under the age of 25. RMSs vary widely in histological appearance and are subdivided into embryonal RMS (E-RMS), alveolar RMS (A-RMS), and pleomorphic RMS (P-RMS).[1]

E-RMS occurs predominantly in the regions of head and neck, genitourinary tract, and retroperitoneum and is most common in children. Several E-RMS have been examined cytogenetically and no consistent abnormalities have yet been described.[26]

A-RMS is less frequent than E-RMS and afflicts adolescents and young adults. The anatomical distribution is similar to E-RMS except for more frequent occurrence in the extremities. A t(2;13)(q35–37;q14) has been observed nonrandomly in A-RMS, in 2 cases as the sole abnormality in populations of cells.[26–28] Sixty-eight percent of A-RMS contain the translocation and an additional 21% show variant rearrangements affecting 13q14, including 14% with a t(1;13)(p36.1;q14).[26] One case of a variant translocation involving 2q37 has been reported in an A-RMS.[29]

The t(2;13) of A-RMS has recently been molecularly characterized by Barr and colleagues.[30] The translocation disrupts the *PAX3* paired box gene on chromosome 2 and juxtaposes it with a forkhead domain gene on chromosome 13. The translocation results in a fusion transcript, encoding a putative chimeric transcription factor, consisting of exons from the 5′ end of *PAX3*, which encode the DNA-binding region, joined to exons from the transcription factor gene on chromosome 13 designated *ALV* or *FKHR* encoding a portion of the forkhead DNA-binding domain and other C-terminal regions.[30,32]

P-RMS is the least common entity and may occur at any age, although its peak incidence is in patients older than 45 years. It typically involves the extremities. Diagnosis is difficult because of the absence of rhabdomyoblasts with cross-striations and its close resemblance to other pleomorphic sarcomas.[1] Cytogenetic analyses of P-RMS have failed to reveal any characteristic abnormality.[26]

Leiomyosarcoma

Leiomyosarcomas (LMSs) are malignant neoplasms that arise from smooth muscle tissue. They are principally tumors of adult life occurring most frequently in the female genital tract and the gastrointestinal tract. These tumors are more common in women than men. LMS are very aggressive with a high recurrence rate and frequent metastasis.[1]

Characteristic chromosomal abnormalities have not yet been described in LMS. The 42 tumors analyzed showed a diverse karyotypic picture with no single change common to all or most LMS.[33,34] Hypodiploidy appeared to be a common occurrence and consistent changes in this group included monosomies of chromosomes 16, 18, and 22 and recurrent structural aberrations of chromosome 1 at bands 1p13-pter such that there was partial monosomy of 1p, which suggests that loss of tumor suppressor genes from these regions may be responsible for tumorigenesis in a subset of these neoplasms. The higher ploidy tumors contained deletions of 3p11-p22. In relation to site, all five LMS of the knee examined cytogenetically showed extra copies of chromosome 20. In general, certain chromosomal breakpoints were identified as being recurrently rearranged. Those most frequently involved were 1p13–36, 7p11–21, 1q32, 13q14 and 14p11.[33]

Extraskeletal Chondrosarcoma

Cartilaginous neoplasms are very diverse with respect to clinical presentation, morphology, and biological behavior, often requiring a multidisciplinary approach to establish diagnosis. Extraskeletal chondrosarcomas (CS) exhibit a broad morphological spectrum and may be myxoid, mesenchymal, or rarely, well differentiated.[1]

Literature on the cytogenetics of CS is scarce; only 39 tumors with clonal chromosomal abnormalities have been reported.[15,35–38] Only the myxoid type has been demonstrated to contain a specific chromosomal alteration. Of 11 extraskeletal myxoid CS analyzed, 3 contained a reciprocal t(9;22)(q22;q11–12), including a case with a complex translocation.[35] In one case it was the sole anomaly.

Twenty-eight CS were classified as grades 1–3.[2,15,37,38] Among these, 7 were trisomic for chromosome 7 and 6 were trisomic for chromosome 8; in 2 cases each the trisomies were the sole abnormality.

Extraskeletal Ewing's Sarcoma and Peripheral Neuroectodermal Tumors

Ewing's sarcoma (ES) is the second most common bone malignancy affecting adolescents and young adults and occurs most commonly in the long tubular bones of the upper and lower extremities. It may also occur as a primary soft tissue neoplasm without involvement of the bone. Extraskeletal ES chiefly involves the soft tissues of the paravertebral region, the adjacent chest wall, retroperitoneum, and the lower extremities. Distinction from other round cell sarcomas such as primitive forms of RMS or neuroblastoma is often difficult by light microscopy.[1]

ES of both skeletal and extraskeletal origin are characterized by a specific t(11;22)(q21–24;q11–13).[2,15,39–41] This translocation seen in 86% of the tumors was reported as the sole abnormality in 17 tumors, suggesting that it is the primary karyotypic abnormality in ES. Seven percent of tumors exhibited complex translocations. Variant translocations involving 22q11–12 were present in 8% of the tumors. Trisomy 8 and der(16) t(1;16)(q11–25;q11.1–24) were identified as the most frequent nonrandom secondary changes in 25% and 11% of the tumors,[6,42,43] respectively.

Peripheral neuroepithelioma (PN) is a malignant tumor whose histological appearance is similar to that of neuroblastoma (NB) but, in contrast to NB, it typically presents in older children and young adults, is sometimes associated with peripheral nerves, and spares the adrenal gland and sympathetic ganglia.[1] Histological and immunohistochemical overlap between ES and PN has long suggested that the two entities may form a continuum.[39]

PNs exhibit a consistent translocation t(11;22)(q23–24;q11–12) that is cytogenetically indistinguishable from the one present in ES. To date 23 tumors have been analyzed, and the translocation was observed in 20 (87%).[6,39,41,43,44] In the remaining 13%, variant translocations involved either 22q11.2–12 (9%) or 11q23 (4%).

Askin's tumor (AT) is a malignant small round cell tumor of the thoracopulmonary region which appears morphologically and immunophenotypically closely related to PN. The tumors occur in children, tend to recur locally, and have a poor prognosis.[1]

Eight ATs have been studied cytogenetically and in 6 a highly specific t(11;22)(q24;q12) identical to that found in ES and PN was identified.[15,41,45,46] The other 2 tumors had involvement of 22q11–12 in variant rearrangements.[29,45] The finding of a similar translocation in the 3 tumor types suggests that they may have a common histogenetic origin with varying histopathological and clinical manifestations.

A t(11;22)(q24;q12) has also been found in an esthesioneuroblastoma (EN),[47] a very rare tumor originating in the neuroectodermal stem cells of the olfactory epithelium. The uniqueness of this marker suggests that all these tumors (ES, PN, AT, EN) may be derived from the same cell type. A neuroendocrine tumor of the small intestine with a t(11;22)[48] and a small cell osteosarcoma (SCOS) with a t(11;22)(q24;q12)[49] have also been described. SCOS is a tumor that resembles ES and is often diagnostically confused with it. Diagnosis is based on the presence of osteoid, but detection of tumor osteoid is not always possible particularly when small biopsies are received for examination. The observation of a t(11;22) in a SCOS thus remains to be confirmed in other cases or verified by molecular means (see below).

ES, PN, and AT all contain a similar specific t(11;22)(q24;q12). The recent molecular characterization of the ES and PN t(11;22) showed that most chromosome 22 breakpoints were clustered within a small 7-kb region, designated EWSR1, within the *EWS* gene, and a larger 40-kb region, EWSR2, within the *FLI1* gene on chromosome 11.[41] Rearrangements of the *EWS* gene (the EWSR1 region) have been demonstrated by Southern blotting in almost all tumors tested, including variant or complex t(11;22).[41,50,51] The translocation leads to the generation of a hybrid transcript from the fusion of the *EWS* and *FLI1* genes.[52] The *FLI1* gene is a member of the *ETS* family of transcription factors and contains a sequence-specific DNA-binding domain[53] whose normal function remains obscure. *EWS* is a novel gene whose normal function is also unknown. One portion appears to encode an RNA-binding domain.[52] How the chimeric *EWS/FLI1* gene product leads to the neoplastic transformation of ES precursor cells is an object of intense interest. Studies using an *in vitro* model system have shown that the *EWS/FLI1* chimeric gene product can induce the neoplastic transformation of NIH 3T3 fibroblasts and that its transforming ability is dependent on the presence of both gene components.[54]

Thus, there are striking structural similarities between three of the four chromosomal translocation breakpoints cloned so far in sarcomas: the t(11;22) of ES/PNET, the t(12;22) of CCS, and the t(12;16) of M-LPS; all result in the rearrangement and fusion of a gene with an RNA-binding domain (*EWS*, *TLS*) with a

transcription factor gene (*FLI1*, *ATF1*, *CHOP*). This pattern is unlike any translocation cloned from hematological tumors, and whether it represents a general model for sarcoma-associated translocations remains to be seen.

Congenital Fibrosarcoma

Congenital or infantile fibrosarcoma (CFS) is a rare, rapidly growing, low-grade soft tissue sarcoma. It chiefly affects the distal regions of the extremities in infants and children. The clinical behavior is more favorable than its adult counterpart. Distinction between aggressive fibromatosis, a benign fibrous tumor which also occurs in infants, and CFS is difficult histopathologically.[1]

Cytogenetic analysis of CFS has revealed nonrandom gains of chromosomes in similar combinations; the chromosomes usually involved are 11, 17, and 20.[55] The findings appear to suggest that trisomy 11 is the important event, because in the 7 cases studied cytogenetically to date, trisomy 11 was present in 6 (86%). Trisomy 20 was also present in 6 cases, but in 2 tumors it was identified as an additional change in a sideline, whereas the stemline contained trisomy 11. Trisomy 17 was present in 3 cases and in an additional case there was partial gain of chromosome 17 from p12 → qter (43%). Trisomies 20 and 17 could therefore represent nonrandom addition of chromosomes during clonal evolution.

Very few cytogenetic analyses have been reported for adult fibrosarcoma and fibromatosis, but from the data available, it appears that CFS is cytogenetically distinct from these and other mesenchymal tumors.[2,15]

MFH

MFH is the most common soft tissue sarcoma of late adult life. The most common histological types are the storiform-pleomorphic type and the myxoid type. The giant cell, inflammatory, and angiomatoid types are less common.[1]

Karyotypic analyses of MFH have not shown any specific rearrangements. However, nonrandom patterns of abnormalities are evident in the 32 cases reported.[6,11,56] About 59% of the tumors show telomeric associations, rings, and dicentric chromosomes. The pattern is similar to that noted in well differentiated liposarcomas except that the karyotypes are more complex in MFH. An additional 13% contain hsrs and double minute chromosomes (dmins). A clinically important cytogenetic change noted in MFH was a 19p+ marker seen in 31% of the cases. This marker has been associated with an increased tendency for local recurrence paralleled by a high rate of distant metastasis.[56,57] Other nonrandom sites of rearrangement include 1q11, 11p11, and 1p36.

Intra-Abdominal Desmoplastic Small Round Cell Tumor

Intra-abdominal desmoplastic small round cell tumor (IADSRCT) is a recently described clinicopathological entity whose definition is still evolving. Its main features include a predominant intra-abdominal location, nesting pattern of growth, focal rhabdoid features, intense desmoplastic reaction, and immunohistochemical reactivity for epithelial, neural, and muscle markers. The tumor is highly aggressive and shows a predilection for adolescent males. Death usually occurs within 2 years of diagnosis.[58]

Cytogenetic findings in only 5 tumors have been published.[59] Three tumors (60%) showed an identical t(11;22)(p13;q11.2-q12), including one case in which it was present as the sole cytogenetic anomaly. In another case, chromosome 22 was involved in a variant and complex rearrangement with chromosomes 2 and 21. The translocation is thus highly specific for IADSRCT and could prove to be diagnostic for the tumor, distinguishing it from other small round cell tumors such as ES, PN, RMS, neuroblastoma, and lymphoma.

Endometrial Stromal Sarcoma

Sarcomas of the uterus constitute only 3% of uterine neoplasms. Endometrial stromal sarcomas (ESS) are rare uterine neoplasms that represent 26% of uterine sarcomas. Approximately two-thirds are low grade and one-third are high grade variants.[60]

Only 8 tumors with clonal chromosomal abnormalities have been reported to date.[6,34,61,62] Three of these tumors contained a similar reciprocal translocation, t(7;17)(p15–21;q12–21) (38%). In 2 tumors, additional rearrangements included del(11q) and translocation breaks at 7q11. In 2 other tumors, variant rearrangements involved 7p21 and 11q13, respectively. This is the only tumor in which the recurrent abnormality was not seen as the only change; however, finding the identical abnormality in tumors of the same pathology from 3 different laboratories suggests that the t(7;17) is the primary change in ESS.

Hemangiopericytoma

Hemangiopericytomas (HP) are rare mesenchymal tumors of pericytic origin, primarily of adult life, oc-

curring most commonly in the lower extremity, especially the thigh, the pelvic fossa, and the retroperitoneum. The diagnosis of HP and prediction of its clinical behavior may pose considerable problems. The distinction of HP from other neoplasms with prominent vascular patterns is often difficult, and among the many tumors that may mimic HP, MFH, SS and mesenchymal chondrosarcoma are the most important.[1]

Cytogenetic data on this rare tumor are also limited. Only 10 tumors, including 2 recurrences, have been analyzed.[63–65] An identical t(12;19)(q13;q13) has been reported in 2 cases thus far (20%): a retroperitoneal HP with the translocation as the only abnormality and a recurrent intracranial HP. In another case, a complex t(6;12;19)(p21;q13;p13) was noted. Both bands 19q13.3 and 12q13 have each been involved in variant rearrangements in an additional 30% of tumors. Perhaps analysis of additional cases will reveal more tumors with a t(12;19)(q13;q13) and define a cytogenetic subtype.

Mesothelioma

Malignant mesothelioma (MM) is a tumor of adult life that mainly affects persons between 50 and 70 years of age and occurs slightly more commonly in men. It arises from the mesothelium of the pleura, peritoneum, and other sites. Histologically 3 types are distinguished: epithelial, fibrous, and mixed. Most MM are associated with exposure to asbestos; the risk of MM increases with asbestos dust concentration, duration of exposure, and the type of fibers.[1]

Numerous cytogenetic studies have been performed in MM.[2,15,66,67] Most tumors are characterized by multiple, complex, and heterogeneous chromosomal aberrations, although a few tumors with single chromosome changes have also been described. Our analysis of published cases revealed deletion of the short arm of chromosome 3 to be the most common. Del(3)(p13–23) was seen in 48% of the cases, closely followed by rearrangements of 1p11–22 in 42%. Other nonrandom aberrations included deletions of 9p, 6q, monosomy 22, and rearrangements of 2p and 12q. Perhaps the 3p abnormalities are causally related to the development of this malignancy. Del(6q) was observed as the sole abnormality in one case, prompting the suggestion that it might represent a primary change.[68]

Clinical correlations have demonstrated an association between the high content of asbestos fibers in lung tissue and partial or total losses of chromosomes 1 and 4 and rearrangements at 1p11–22. Copy number of 7p was suggested to be a prognostic factor; the higher the 7p copy number, the shorter the survival time.[69]

Recurrent Chromosomal Aberrations in Benign Soft Tissue Tumors

Cytogenetic analyses of benign tumors have dispelled the myth that chromosomal aberrations are associated solely with malignancy. Benign neoplasms of mesenchymal origin studied in detail include lipomas and uterine leiomyomas. Studies of these two tumor types have contributed greatly to our knowledge of the karyotypic picture in benign tumors and made us aware of the cytogenetic diversity inherent in these tumors.

Lipoma

Lipomas are benign neoplasms of adipose tissue and represent the most common mesenchymal neoplasm in humans. They may be single or multiple, superficial or deep-seated. Lipomas do not metastasize and recurrences are local and nonaggressive. Malignant transformation is very rare.[1]

Lipomas have been studied extensively with over 300 tumors being characterized cytogenetically.[20,70–76] Based on clonal abnormalities, cytogenetic groups have been delineated composed of tumors with abnormalities involving chromosome region 12q13–15 and those with other clonal aberrations. Rearrangements of 12q13–15 are seen in about 59% of the tumors primarily due to consistent translocations of 12q13–15 with 3q27–28, 1p32–34, 21q21–22, 2p21–23, and other nonrecurrent rearrangements. Abnormalities not involving 12q13–15 include lipomas with deletion 13q, ring chromosomes, and rearrangements of 6p21–23, 11q13, and 1p36.

Uterine Leiomyomas

Uterine leiomyomas are benign mesenchymal tumors of the uterus found characteristically in women between the ages of 30 to 40 years. They are the most common uterine neoplasms, occurring in 20 to 30% of women. Leiomyomas are usually multiple. Their etiology is unknown, but they are known to be hormone-dependent tumors whose size and growth are apparently influenced by estrogen and progesterone. They do not undergo malignant transformation.[1]

Uterine leiomyomas have also been cytogenetically analyzed in great numbers, with over 500 tumors studied.[15,77–85] More than 200 tumors contained

clonal chromosomal aberrations, many of which were recurrent. The two most common abnormalities were del(7)(q11.2–22q31–32) found in 35% of the tumors with anomalies and t(12;14)(q14–15;q23–24) seen in 20% of the tumors. Both abnormalities have been identified as the sole change in a number of tumors, suggesting that more than one mechanism operates in the development of uterine leiomyomas. Variant translocations involve both chromosomes 12 (10%) and 14 (5%). Trisomy 12 and del(13)(q12q33) have been seen in smaller proportions of tumors also as sole anomalies or in addition to other changes. Additional recurrent abnormalities include monosomy 22, the presence of ring chromosomes, and rearrangements of 1p36 and 6p21.

Endometrial Polyp

Endometrial polyps contain variable admixtures of epithelial glands, mesenchymal stroma, and blood vessels. Their size varies from small masses to a large growth that fills the endometrial cavity. They are characteristically found in women between 40 and 50 years of age and most are asymptomatic. Their neoplastic nature has not been clearly established. Carcinomas have, however, been reported in a small percentage of polyps.[1]

Clonal cytogenetic abnormalities have been described in only 8 endometrial polyps.[86] Five of these tumors showed a rearrangement involving chromosome band 6p21; in 2 polyps an identical t(6;20)(p21;q13) was present. The other 3 tumors showed rearrangements of chromosome 12 at bands q13–15; in 2 cases the inv(12) abnormality was morphologically similar, although the interpretation of the breakpoints was different, p11.2 and q13 and p12–13 and q14–15. Thus 2 cytogenetic subgroups appear to characterize endometrial polyps.

Desmoid Tumors

Desmoid tumors are lesions of uncertain histopathogenesis that arise from the connective tissue of muscle and the overlying fascia. They present a problem in recognition and management because of a deceptively harmless microscopic appearance and a potential to attain a large size, recur, and infiltrate neighboring tissues causing considerable morbidity. The peak incidence is between ages 25 and 35 and the principal location is the musculature of the shoulder, chest wall, back, and thigh.[1] Desmoid tumors may occur as a feature of Gardner's syndrome, the gene for which (*APC*) has been localized to 5q21–22.[87] The role of the *APC* gene in the origin of desmoid tumors of Gardner's syndrome has not yet been examined.

Clonal karyotypic abnormalities have been observed in 8 cases and in 5 other cases striking telomeric association was observed.[88] Clonal deletions of 5q, del(5)(q13–31), del(5)(q14q21), del(5)(q23.1), were observed in 23% of the tumors. The long arm of 5q may have an important role in the genesis of desmoid tumors similar to that in colon carcinogenesis.

Loss of Heterozygosity and Gene Amplification in Soft Tissue Tumors

Although loss of heterozygosity (LOH) and gene amplification are usually studied by molecular approaches, both types of changes have cytogenetic counterparts. The detection of recurrent cytogenetic deletions is often useful in targeting specific areas of the genome for LOH studies. Likewise, gene amplification is recognized cytogenetically as dmins or hsrs, and various molecular strategies now exist for isolating the amplified sequences from these regions. These alterations occur in selected soft tissue sarcomas with less tumor type specificity than translocations. They are therefore discussed collectively here.

LOH studies over the past few years have led to an almost exponential accumulation of data. The tumor suppressor genes best studied in sarcomas are *TP53* and *RB1* at 17p13 and 13q14, respectively. They have been studied extensively for point mutations in the case of *TP53* and deletions and rearrangements in the case of *RB1*. Both genes have also been analyzed at the level of mRNA expression in many sarcomas.

Inactivation of *RB1* by partial or complete deletion or mutation has been reported in various types of high grade soft tissue sarcomas unrelated to hereditary retinoblastoma, including leiomyosarcomas, LPS, MFH, and malignant peripheral nerve sheath tumors (MPNST).[89–91] Within these tumor types, it remains unclear whether it is a minority or a majority of cases that lose normal *RB1* function.[89,91]

The *TP53* gene is involved in the tumorigenesis of several sarcomas. LOH for chromosome 17p region and/or *TP53* point mutations have been demonstrated in MFH, LMS, LPS, MPNST, mesothelioma, and RMS, among others, in frequencies ranging from 30% to more than 70%.[92–94] Genetic alterations of *TP53* are diverse, consisting of point mutations, which usually result in loss of function with dominant negative effects and commonly lead to overexpression of abnormal p53 protein, and deletions, which lead to its

Table 2. *Diagnostic Utility of Specific Translocations in Sarcomas*

Histology	Characteristic Cytogenetic Abnormality	Diagnostic Relevance
Synovial sarcoma	t(X;18)(p11.2;q11.2)	Yes
Clear cell sarcoma	t(12;22)(q13-14;q12-13)	Yes
Myxoid liposarcoma	t(12;16)(q13;p11)	Yes
Alveolar rhabdomyosarcoma	t(2;13)(q35-37;q14)	Yes
Ewing's sarcoma/Askin's tumor/peripheral neuroepithelioma	t(11;22)(q21-24;q11-13)	Yes
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q11-12)	Yes
Intra-abdominal desmoplastic small round cell tumor	t(11;22)(p13;q11.2-12)	Yes
Endometrial stromal sarcoma	t(7;17)(p15-21;q11.2-21)	?
Hemangiopericytoma	t(12;19)(q13;q13.3)	?

absence.[95,96] The p53 protein may normally function as a homotetramer and is currently thought to be involved in the transcriptional control of genes in the cellular response pathway to DNA damage, a pathway which may lead either to an arrest in G1 to effect DNA repair or to apoptosis.[95,96] The relevance of the *TP53* gene to sarcomagenesis is further underscored by the frequent occurrence of bone and soft tissue sarcomas in Li-Fraumeni syndrome,[97,98] which is characterized by constitutional mutations of *TP53*. In several instances, inactivation of both *TP53* and *RB1* in the same tumor has been demonstrated, suggesting that the coincident loss of function of more than one of these genes may be necessary for the development of at least some sarcomas.[99]

Recently, another important mechanism of p53 inactivation has been reported in sarcomas. Amplification of the *MDM2* gene, which encodes a p53-binding protein,[100] may result in functional inactivation of the p53 protein. The product of this gene appears to act normally as a regulator of p53 protein function.[100,101] The *MDM2* gene has been found to be amplified in several types of sarcomas, including MFH, LPS, and osteosarcomas.[100,102] Interestingly, these two modes of p53 protein inactivation, namely *TP53* gene alterations and *MDM2* amplification, appear to be mutually exclusive genetic events in the genesis of most sarcomas tested.[103] The *MDM2* gene maps to 12q13, the site of other genes previously reported to be amplified in sarcomas, such as *GLI* and *SAS*.[104,105] It is likely that these genes are coamplified on a single large amplification unit.

Comment

Human cancer encompasses many diverse diseases with varying etiology, biology, clinical presentation, and prognosis. Reflecting this diversity is the wide spectrum of karyotypic changes, some specific and some random. The specificity of some of the chromosomal aberrations has led to the recognition of cytogenetics as an essential adjunct to conventional diagnostic pathology and provides the clinician and the pathologist with an additional modality in the diagnosis of malignant soft tissue tumors and allows a broader base for a histogenetic classification of these tumors. Progress in this area has been slow but steady. However, over the last 2 years, major advances have been made with the identification of specific translocations in many rare sarcomas, and continued analysis will probably lead to similar characterization of other tumors. Karyotypic analyses have been particularly helpful in the differential diagnosis of histologically similar small round cell tumors which are composed of primitive cells that often lack distinguishing features and include neuroblastoma, RMS, ES, PN, AT, and lymphoma. Each of these tumors contains specific chromosome changes, and therefore cytogenetic analysis provides an excellent approach that can reliably distinguish between these neoplasms (Table 2). In addition, the identification of diagnostic chromosome translocations in histologically undifferentiated tumors may support a diagnosis that is doubtful on histological grounds alone or may even lead to a reconsideration of the histological diagnosis. The role of cytogenetics in determination of prognosis has not been fully explored in soft tissue sarcomas. Prospective studies with detailed follow-up will help to provide information in this area. Finally, the cloning of the breakpoints of specific sarcoma-associated translocations is opening up new opportunities in molecular diagnosis, detection of minimal disease, and further basic investigation into the biology of these tumors.

Note Added in Proof

We have recently found that the t(11;22)(p13;f12) in IADSRCT involves the *EWS* gene at 22q12 and the

WT1 gene at 11p13, and results in a *EWS-WT1* chimeric mRNA (Ladanyi M, Gerald W, Cancer Res 1994, in press).

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