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REVIEW ARTICLE

Angelo P. Dei Tos · Paola Dal Cin

The role of cytogenetics in the classification of soft tissue tumours

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Abstract Soft tissue tumours represent a heterogeneous group of mesenchymal lesions, and their classification is the subject of continuous debate. Chromosome analysis, molecular cytogenetics and molecular assays may become increasingly useful in diagnosis, and this review summarises advances in the cytogenetic characterisation and classification of soft tissue tumours. Among the group of fibrous lesions, superficial fibromatosis exhibits trisomy 8. This genomic change is also observed in desmoid fibromatosis in association with trisomy 20. Trisomy 11 is the most frequently observed chromosomal aberration in congenital fibrosarcoma. Dermatofibrosarcoma protuberans and giant cell fibroblastoma share a translocation t(17;22), which supports the concept of the existence of a common differentiation pathway. Adipose tissue tumours is the group in which integration of genetics and pathology has been most fruitful. Ordinary lipomas cytogenetically show an abnormal karyotype in about half the cases. Genomic changes of the 11q13 region are observed in hibernoma. Lipoblastoma exhibits a specific 8q rearrangement in 8q11-q13. Loss of material from the region 16q13-qter and 13q deletions are observed in spindle cell/pleomorphic lipomas. The well-differentiated liposarcoma/atypical lipoma group is characterised karyotypically by the presence of one extra ring and/or extra giant chromosome marker. Myxoid and round cell liposarcoma share the same characteristic chromosome change: t(12;16)(q13;p11) in most cases. In the group of smooth muscle lesions most data are derived from uterine leiomyomas, which can be subclassified cytogenetically into seven different types. Half of all leiomyomas are chromosomally normal; the other half have one of six possible consistent chromosome changes. Alveolar rhabdomyosarcoma is characterised cytogenetically by two variant translocations t(2;13)(q35;q14) and t(1;13)(p36;q14). Among tenosynovial tumours, the localised type of giant cell tumour of tendon sheath exhibits two different karyotypic changes. One involves 1p11 in a translocation with chromosome 2 or with another chromosome. A second type involves 16q24. Synovial sarcoma is characterised cytogenetically by a translocation occurring between chromosome 18 and presumably two adjacent loci on the X chromosome. In neural tumours, abnormalities of chromosome 22 have been reported in benign schwannomas and perineuriomas. Malignant peripheral nerve sheath tumours exist in two main forms: sporadic and associated with the NF-1 syndrome. Karyotypes are very complex, but chromosomes 17q and 22q are very often involved. Clear cell sarcoma is characterised cytogenetically and molecularly by a translocation t(12;22)(q13;q12). The Ewing's sarcoma/peripheral neuroectodermal tumour category shows a central karyotypic anomaly represented by the translocation t(11;22). The two variants t(21;22) and t(7;22) are found in some cases. Among cartilaginous lesion, the most frequently described anomaly is the t(9;22)(q22;q12) in extraskeletal myxoid chondrosarcoma. Intra-abdominal desmoplastic small round cell tumour is characterised by a t(11;22)(p13;q12).

Key words Soft tissue tumours · Classification · Cytogenetics

A.P. Dei Tos (✉)
Department of Pathology, City Hospital, I-31100 Treviso, Italy
Fax: (39) 422-32 26 63

P. Dal Cin
Centre for Human Genetics, University of Leuven,
Leuven, Belgium

Introduction

Soft tissue tumours are a heterogeneous and complex group of mesenchymal lesions, which may show a broad range of differentiation [35, 39, 40]. The WHO classification recognises benign, malignant and borderline (locally aggressive, nonmetastasising) categories [108]. The histological classification is based upon morphological demonstration of a specific line of differentiation but, despite the contribution of ancillary diagnostic techniques such as electron microscopy and immunohistochemistry,

the classification of mesenchymal neoplasms is still the subject of continuous debate.

Correct recognition of soft tissue tumours represents an essential prerequisite for proper treatment and any auxiliary method able to improve both the sensitivity and specificity of current diagnostic procedures is important. As with leukaemia two decades ago [80], chromosome analysis, molecular cytogenetics and molecular assays may become increasingly useful in the diagnostic approach to solid tumours in general, and to soft tissue tumours in particular.

Genomic changes in soft tissue tumours

For the purpose of uniformity the WHO system, which classifies the more than 200 entities in distinct subgroups will be followed [108]. Nonetheless, major contrasts concerning tumour classification will be addressed specifically. Indications will be given in this overview on where reliable information on genomic changes is already available for each of the groups (Tables 1, 2).

For further details on this topic the reader is also referred to more detailed sources that focus on genomic aberrations in neoplastic disease [75, 90] and in soft tissue tumours [11, 31, 42, 91, 102, 106] as well as on molecular analysis [62, 67] and pathology of soft tissue tumours [35, 39, 40].

Fibrous tissue tumours

Clinically, five subcategories of fibrous lesions can be distinguished: reactive processes such as nodular fasciitis, hamartomatous lesions, benign and locally aggressive tumours, and true malignancies. Histologically, fibrous tumours are actually composed usually of a variable admixture of fibroblasts and myofibroblasts [69].

In the group of reactive/benign processes few cases have been investigated cytogenetically, and normal karyotypes or inconsistent changes have been observed. Among the fibromatoses, however, a group of locally aggressive nonmetastasising neoplasms which are characterised by infiltrative, destructive growth, the superficial palmar and plantar variants (also known under the eponyms of Dupuytren's and Ledderhose's diseases, respectively) exhibit trisomy 8, which is also found in the deep-seated desmoid tumours [7]. In the deeper seated desmoid fibromatoses clones may be found with trisomy 8, others with trisomy 20; and in some other cells both trisomies are present together [87]. In desmoid tumours associated with familial adenomatous polyposis (Gardner's syndrome) 5q rearrangements have been detected which, however, may be more related to the polyposis than to the desmoid tumour [20]. Nonetheless, a role for inactivation of the *APC* gene in the development of desmoid tumours has been postulated [76].

Table 1 Specific (primary) chromosome changes in soft tissue tumours

Benign soft tissue tumours	
Lipoma (ordinary)	t with 12q15/t with 6p21/13q-
Lipoblastoma	t with 8q11-13
Hibernoma	t with 11q13
Spindle cell and pleomorphic lipoma	loss of 16q13-qter
Leiomyoma (uterus)	t with 12q-15/7q-/+12/13q-/ t(1;2)(p36;p24)/t with 6p21/3q-
Giant cell tumour of tendon sheath	t with 1p11/t with 16q24
Schwannoma	–22
Myxoma (cardiac)	t with 12p12
Superficial fibromatosis	+7/+8
Borderline soft tissue tumours	
Atypical lipoma/well-differentiated liposarcoma	+ ring or long marker (sequences 12q13-q15)
Dermatofibrosarcoma protuberans and Giant cell fibroblastoma	t(17;22)(q22;q13); +r (sequences 17q and 22q)
Congenital fibrosarcoma	combination of trisomies (8, 11, 17, 20)
Aggressive angiomyxoma	t with 12q14-15
Desmoid tumours	+8/+20/+8, +20
Malignant soft tissue tumors	
Liposarcoma	t(12;16)(q13;p11)
(myxoid/round cell)	t(12;22)(q13;q12)
Leiomyosarcoma (GI)	Monosomy 1p12-1pter with hypodiploid chromosome number
Rhabdomyosarcoma (alveolar)	t(2;13)(q35;q14)/t(1;13)(p36;q14)
Synovial sarcoma	t(X;18)(p11.2;q11.2)
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22-q31;q12)
Ewing's sarcoma/PNET	t(11;22)(q24;q12)t(21;22)(q22;q12) t(7;22)(p22;q12)
Clear cell sarcoma	t(12;22)(q13;q12)
Desmoplastic small round cell tumour	t(11;22)(p13;q12)
Alveolar soft tissue sarcoma	t with 17q25

Table 2 Molecular genetics in soft tissue tumours

Translocation	Tumour	Affected gene
t(11;22)(q24;q12)	Ewing sarcoma/PNET	*FLI1* (11q24) *EWS* (22q12)
t(21;22)(q22;q12)	Ewing sarcoma/PNET	*ERG* (21q22) *EWS* (22q12)
t(7;22)(p22;q12)	Ewing sarcoma/PNET	*ETV1* (7p22) *EWS* (22q12)
t(12;22)(q13;q12)	Clear cell sarcoma	*ATF1* (12q13) *EWS* (22q12)
t(12;16)(q13;p11)	Liposarcoma (myxoid/round cell)	*CHOP* (12q13) *FUS* (16p11)
t(12;22)(q13;q12)	Liposarcoma (myxoid/round cell)	*CHOP* (12q13) *EWS* (22q12)
t(2;13)(q35;q14)	Alveolar rhabdomyosarcoma	*PAX3* (2q35) *FKHR* (13q14)
t(1;13)(p36;q14)	Alveolar rhabdomyosarcoma	*PAX7* (1p36) *FKHR* (13q14)
t(X;18)(p11.2;q11.2)	Synovial sarcoma	*SYT* (18q11.2) *SSX1* (Xp11.2) *SSX2* (Xp11.2)
t(11;22)(p13;q12)	Desmoplastic small round cell tumour	*WT1* (11p13) *EWS* (22q12)
t(9;22)(q22-q31;q12)	Chondrosarcoma (extraskeletal myxoid)	TEC (9q31) *EWS* (22q12)
t(3;12)(q27;q15)	Lipoma (ordinary)	*HMGI-C* (12q15) *LPP* (3q27)
t(17;22)(q22;q15)	DFSP/giant cell fibroblastoma	*COL1A1* (17q22) *PDGFB* (22q13)
t(12;V)(q15;V)	Benign mesenchymal tumours	*HMGI-C* (12q15)
t(16;V)(p21;V)	Benign mesenchymal tumours	*HMGI-Y* (6p21)

As far as the malignant fibrous tissue tumours are concerned, with the advent of electron microscopy and immunohistochemistry, which allow easier recognition both of monophasic spindle cell synovial sarcoma and of malignant peripheral nerve sheath tumours (MPNST), the adult form of fibrosarcoma is currently regarded as rare [15, 39]. The congenital or infantile fibrosarcoma, which in stark contrast to the adult form, has an 80% 5-year survival rate, has numerical chromosome changes only, with trisomy 11 as the most frequently occurring trisomy [93]. Although not pathognomonic, the chromosome changes in this type of tumour may help in selection of the more adequate treatment.

Fibrohistiocytic tumours

Before analysing the cytogenetic data, it has to be stressed that the term “fibrohistiocytic” is most probably a misnomer. Even if this denomination is retained for the purpose of diagnostic homogeneity, virtually none of the lesions included in this subgroup exhibits true histiocytic differentiation [39]. Moreover, strong arguments have been raised recently against the very existence of the clinically most relevant subtype of sarcoma belonging to this category: the storiform and pleomorphic variant of malignant fibrous histiocytoma (MFH) [38]. Pleomorphic MFH, once the most commonly diagnosed sarcoma, probably reflects a histological feature common to a variety of unrelated high-grade malignancies, in which a recognisable line of differentiation is demonstrated by adequate sampling and by the application of ancillary diagnostic procedures. The MFH category, in addition to the prototypic storiform and pleomorphic variant, includes myxoid (myxofibrosarcoma), giant cell and inflammatory subtypes. Myxofibrosarcoma (myxoid MFH) is a distinctive clinicopathological entity, which exhibits a broad spectrum of histological grades but in which fibroblastic or focal myofibroblastic differentiation alone can be demonstrated [73]. As far as the giant cell and inflammatory variants are concerned, they most probably represent a heterogeneous group of malignancies [39, 71].The angiomatoid variant, a lesion that clinically tends to occur in a younger age group and which histologically may exhibit myoid differentiation [37], has been moved in the WHO classification from the malignant to the borderline category [108].

No consistent karyotypic changes have so far been reported in the benign tumours belonging to this group. In MFH, karyotypes are mostly abnormal and complex, perhaps with involvement of the 19p13 region [63], but this finding is largely meaningless as it refers to a broadly heterogeneous group of unrelated lesions.

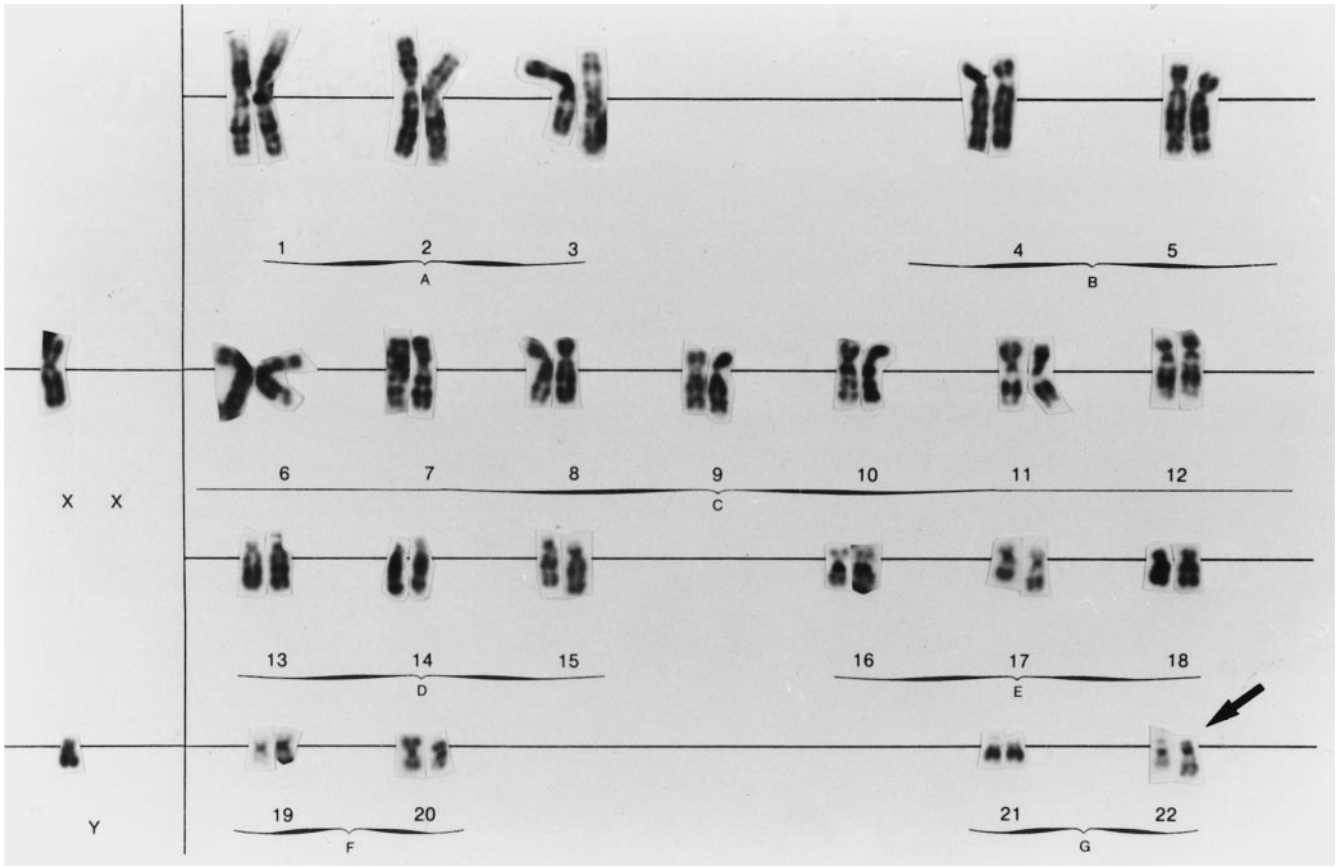

Fig. 1 G-banded karyotype showing der(22)t(17;22)(q21,q13) (*arrow*) represents a characteristic chromosome change in giant cell fibroblastoma

In the group of so-called intermediate malignancy two tumours are progressively becoming characterised genetically. Dermatofibrosarcoma protuberans (DFSP) is a low-grade dermal neoplasm with a tendency to recur; in a minority of cases it may undergo tumour progression with acquisition of metastatic potential. Cytogenetically, DFSP shows extra ring (80%) or extra marker (20%) chromosome(s) in which material from chromosomes 17 and 22 is involved [78]. Giant cell fibroblastoma (GCF), a dermal lesion mainly occurring in infants and young children, has been shown to demonstrate a t(17;22) (Fig. 1). In both tumours this translocation leads to the fusion of the platelet-derived growth factor B-chain (*PDFGB*) gene with the collagen type 1α1 (COL1A1) [98]. Interestingly, the coexistence of DFSP and GCF has been described repeatedly along with CD34 immunopositivity in both lesions [4, 94]. Cytogenetic data support the concept that GCF and DFSP represent closely related entities [17].

Adipose tissue tumours

The tumour types in which integration of genetics and pathology has been most fruitful are the adipose tissue tumours. Full credit must be given to the work carried out by a cooperative group named CHAMP (CHromosome And MorPhology), which includes cytogenetists, clinicians and pathologists from Europe and United States [41, 64, 89, 97, 103].

Lipomatous tumours are the most common soft tissue lesions encountered by every practising surgical pathologist. Numerous variants exist, both in the benign and in the malignant category, which may pose diagnostic problems. A thoughtful review focusing upon the most important conceptual problems concerning adipocytic tumours and summarising the contribution of cytogenetics has been published recently in this journal [68]. More data concerning the molecular aspect of the genomic changes observed in adipocytic tumours have been published recently and deserve comment.

Ordinary lipomas usually represent a straightforward diagnosis. In contrast, cytogenetically half of all cases have an abnormal karyotype. Three main subgroups can be identified: (1) a major group involving 12q13-15, with several possible partners, of which 3q22 is a preferential one; (2) a deletion of 13q; and (3) a rearrangement of 6p21-22.

The target gene in 12q-15 is a member of the High Mobility Group Protein (HMG) gene family [2, 92], HMGI-C, which, in its preferential translocation with # 3, fuses its DNA-binding domains to the protein-binding interfaces of the protein of a gene called *LPP*, which shows sequence similarity to the LIM protein family

[86]. The members of this family all possess so-called LIM domains (i.e. cysteine-rich, zinc-binding protein sequences found in transcription regulators, proto-oncogene products and adhesion plaque constituents), which seem to play some part in cell signalling and control of cell fate during development [92]. HGM proteins are divided into three distinct families, the HMG box containing HMG1/HMG2, the active chromatin-associated HMG14/HMG17, and the HMGI proteins [49]. At present, the last family consists of three genes, *HMGI, HMGI(Y)* and *HMGIC*. In humans, some members of the *HMG* family have been localized. For instance, *HMGIC* is mapped to 12q15, *HMGI(Y)* to 6p21, *HMG17* to 1p36.1–35, *HMG14* to 21q22, *HMG1L* to 13q12, and *HMG2* to 4q31; all these are chromosome regions involved in mesenchymal benign tumours or in tumours with a mesenchymal component.

In addition to lipomas, the *HMGIC* gene was shown to be disrupted in uterine leiomyomas, salivary gland tumours and pulmonary chondroid hamartomas [55, 92]. Recently, rearrangements of the *HMG(Y)* characterised by involvement of 6p21 have been demonstrated in benign mesenchymal tumours such as uterine leiomyomas [56, 57].

Hibernoma is a rare benign tumour, mostly occurring in the interscapular region of adults; its histological hallmark is the presence of brown fat. Cytogenetically the 11q13 region has been involved in all cases examined [74].

Lipoblastoma is also a rare tumour, occurring most commonly in infants and young children. Lipoblastoma can mimic myxoid liposarcoma morphologically and, when it occurrs in adolescents, the differential diagnosis becomes really challenging [70]. The identification of a specific 8q rearrangement in 8q11-q13, as opposed to the 12;16 translocation seen in myxoid liposarcoma, indicates the benign nature of the tumour so that overtreatment can be avoided [13].

Spindle cell/pleomorphic lipomas represent a group of lesions characterised by a somewhat overlapping clinical and morphological picture. Predominant occurrence in the shoulder and neck region of middle-aged men is reported [39]. The characteristic chromosome change represented by loss of material from the region 16q13-qter, along with 13q deletions [41], supports the concept of spindle cell and pleomorphic lipomas as a spectrum of lesions and also justifies their separation from both benign lipomas and atypical lipomas/well-differentiated liposarcomas.

Angiolipomas occur most often as multiple, sometimes painful, lesions, and interestingly, chromosome changes have not been detected so far [97].

Well-differentiated (WD) liposarcoma represents a group of tumours further subclassified by WHO into adipocytic (lipoma-like), sclerosing and inflammatory subtypes [108]. Recently, a rare spindle cell variant has been described, which fulfils criteria for inclusion under the same heading [23]. Great controversy has been generated by the introduction of the term atypical lipoma or atypical lipomatous tumours. The reader is referred to the paper by Mentzel and Fletcher [68] for a historical reconstruction of this controversy, but we wish to emphasise the concept that well-differentiated liposarcoma and atypical lipoma should be considered as synonyms. Their use should depend on the degree of reciprocal comprehension between the surgeon and the pathologist to prevent either inadequate or excessive treatment.

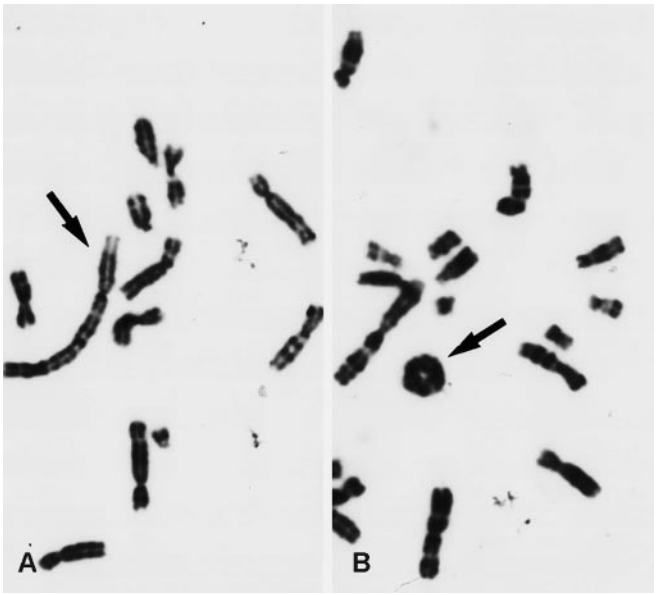

Fig. 2 Partial G-banded metaphases showing **A** the giant chromosome marker and **B** the ring chromosome generally found in atypical lipoma/well-differentiated liposarcoma

Karyotypically these tumours are characterised by the presence of one extra ring and/or extra giant chromosome marker [89] (Fig. 2). At the molecular level, these rings and giant markers proved to present amplifications of the 12q13-15 region [12]. Importantly, gain of 12q material has been detected in a case of spindle cell liposarcoma, which supports the inclusion of this rare variant in the well-differentiated group [64]. This finding has been confirmed recently in two additional cases (C.D.M. Fletcher, unpublished observations).

Which genes from that region are amplified is not yet totally elucidated but among the possible and known candidates *GLI* (*GLI*oblastoma), *CHOP* (*C*CAAT/enhancer-binding protein *HO*mologous *Pr*otein), *ATF1* (*A*ctivating *T*ranscription *F*actor *1*), *SAS* (*S*arcoma *A*mplified *S*equence), *CDK4* (*C*yclin-*D*ependent *K*inase *4*), and *MDM2* (*M*urine *D*ouble *M*inute *2*), the last three may be especially involved, but the amplification pattern is not consistent in all tumours.

Dedifferentiated liposarcoma is considered by WHO as a distinct type of liposarcoma, in which transition from low-grade to high-grade morphology within a WD liposarcoma is observed. First described by Evans in 1979 [36], such a phenomenon may occur either in the primary tumour (de novo) or in recurrences. Surprisingly, the clinical outcome of dedifferentiated liposarcoma

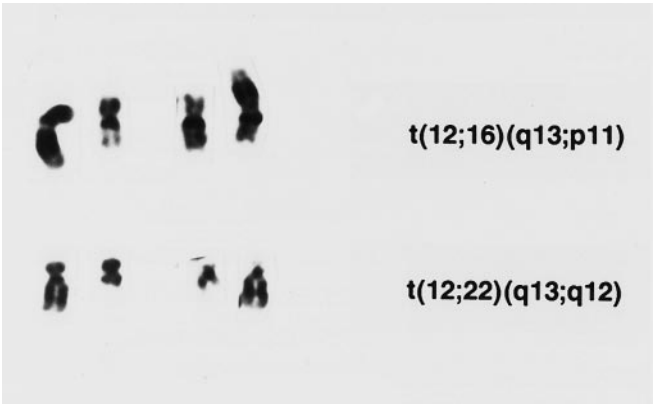

Fig. 3 Partial G-banded karyotypes showing t(12;16(q13;p11) and its variant t(12;22)(q13;q12), found in myxoid and round cell liposarcomas

is less aggressive than that of other high-grade pleomorphic sarcomas [66]. Interestingly, in stark contrast with the complex karyotypic aberration observed in pleomorphic sarcomas, dedifferentiated liposarcoma usually exhibits the same cytogenetic anomalies as WD liposarcoma [41]. At the molecular level, overexpression of *MDM2* has been observed along with integrity of the *p53* gene in the majority of cases [26]. A significant increase in the level of both *MDM2* overexpression and amplification in the high-grade areas has been observed, which may account for the tumour progression in this subset of sarcomas [26, 79].

Myxoid and round cell liposarcoma, even if still sometimes classified as two distinct subtypes, share both clinical and morphological features. Lesions combining both patterns are relatively frequent, and it is widely agreed that round cell liposarcoma can be considered the high-grade counterpart of myxoid liposarcoma. Furthermore myxoid and round cell liposarcoma share the same characteristic chromosome change: t(12;16) [9, 59, 60]. At the molecular level fusion occurs between the *CHOP* gene on 12q13, which belongs to the CCAAT/enhancer-binding protein family and is involved in adipocyte differentiation, and the *FUS* (or *TLS*) gene on 16p11, which has an RNA-binding domain. The *CHOP* gene is a transcription factor that normally promotes growth arrest (i.e. antiproliferative activity), but the fusion product *CHOP-TLS* fails to induce it. The *FUS* gene shows great homology with the *EWS* gene, both in structure and function. It is not surprising therefore that the only cytogenetic variant of myxoid liposarcoma so far known involves chromosome 12 with *CHOP* and chromosome 22 with *EWS* [19, 82] (Fig. 3). Trisomy 8 has been observed as a non-random secondary change [101].

Smooth muscle tumours

While benign smooth muscle tumours are common, leiomyosarcoma outside visceral soft tissues is much less common. Karyotypic data for both benign and malignant soft tissue smooth muscle tumours are generally sparse, while more information is available for visceral sites.

Uterine leiomyomas, which are often multiple, present seven different types cytogenetically. Half of all leiomyomas are chromosomally normal. The other half has one of six possible consistent chromosome changes. The most common among these involves the 12q14-15 region in a translocation with chromosome 14 as a preferential partner. Equal in frequency is a deletion of 7q, followed by anomalies involving 6p. Much rarer are trisomy 12, translocation t(1;2) and deletions of 3q [16]. Molecularly some information is already available for the 12q region where the *HMGI-C* is involved [92]. There is no information as yet about the molecular changes in the 14 translocation partner or in the other structural abnormalities. With regard to the malignant tumours in this group, leiomyosarcoma of the gastrointestinal tract (malignant gastrointestinal stromal tumour with smooth muscle differentiation) is the only site where chromosome changes have been found. They include hypodiploidy with consistent loss of 22 and a structural change: deletion of 1p11-12 [6].

Whilst karyotypic analysis of soft tissue leiomyosarcoma has not revealed specific genomic changes, molecular analysis has been more fruitful, showing aberrations of the CyclinD1-Rb pathway at the G1-S cell cycle checkpoint in more than 90% of cases, along with rare *p53* gene mutations [22, 25].

Striated muscle tumours

Of the different subtypes into which rhabdomyosarcoma is subdivided (embryonal, spindle cell, alveolar and pleomorphic), alveolar rhabdomyosarcoma is the only one to be well characterised both cytogenetically and molecularly [32, 109]. There are two variant translocations, involving chromosome 13 and either chromosome 1 or 2. Molecularly, the gene involved on 13 is *FKHR* (*F*or*KH*ead *R*elated gene), a putative transcription factor. The genes involved on 1 and 2 are from the PAX (*PA*ired bo*X*) family: *PAX7* on 1 and *PAX3* on 2. The result of the translocations is a novel fusion gene and a chimeric gene product [21, 45].

Interestingly, the solid variant of alveolar rhabdomyosarcoma, which lacks the distinctive alveolar growth pattern, also exhibits the t(2;13) [83]. In embryonal rhabdomyosarcoma, gain of chromosomes 2, 7, 8, 12, 13, 17, 18, and 19 along with loss of chromosomes 10, 14, 15, and 16 was seen by comparative genomic hybridisation [107].

Tenosynovial tumours

Some preliminary information is available on giant cell tumour of tendon sheath. These tumours may occur in a localised or in a diffuse type. In the localised form two

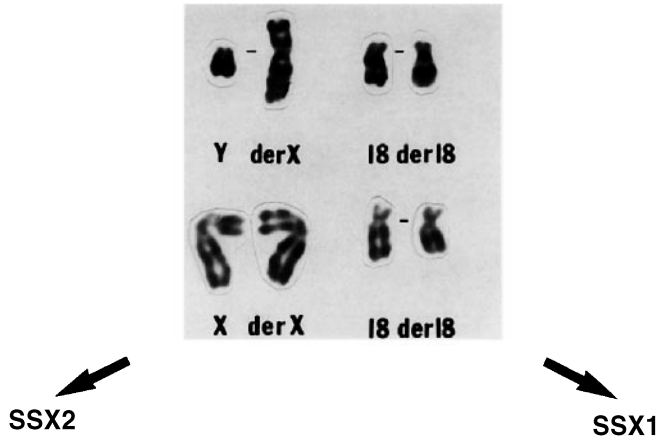

Fig. 4 Both monophasic and biphasic synovial sarcomas are characterised by the same t(X;18)(p11;q11), but the genes involved seem to be different

different karyotypic changes seem to occur. One involves 1p11 in a translocation with chromosome 2 or with another chromosome. A second type involves 16q24 without any obvious preference for a partner chromosome [14]. The diffuse type so far only shows simple but different numerical changes.

Synovial sarcoma, which is not thought to be derived from synovium, is subclassified into two main types: spindle cell monophasic and biphasic, in which a variable number of glandular structures are present. The immunohistochemical coexpression of mesenchymal (vimentin) and epithelial markers (cytokeratins, EMA) is a valuable diagnostic aid. Recently, CD99 and S-100 protein immunoreactivity has been reported, which represents a potential diagnostic pitfalls [24, 50]. Synovial sarcoma is characterised cytogenetically as well as molecularly. Translocation occurs between chromosome 18 and, presumably, two adjacent loci on the X chromosome. One of these translocations may be more associated with the monophasic type, the other with the biphasic type (Fig. 4). The gene involved on chromosome 18 is *SYT* (*SY*novial sarcoma *T*ranslocation), which is unrelated to any other known gene but contains a predicted glutamine-proline-glycine-rich region suggestive of a transcriptional activation domain. The genes involved on the X-chromosome are called SSX_1 (*S*ynovial *S*arcoma *X* breakpoint) and SSX_2 and are also unrelated to other known genes. The translocation leads to the formation of a chimeric transcript as in other sarcoma translocations [8, 43]. It is important to emphasise that synovial sarcoma occasionally shows a primitive, round cell morphology, which may cause diagnostic difficulty. Separation from other spindle cell sarcomas is crucial, because synovial sarcoma is chemosensitive, and cytogenetic analysis is a particularly useful diagnostic tool in this context.

Neural tumours

The range of structure and cell type toward which the so-called peripheral nerve sheath tumours can differentiate is so broad that their classification is very complex and diagnostic criteria somewhat imprecise. Furthermore, there are tumours that show clear-cut neuroectodermal differentiation but for which demonstration of their origin from a peripheral nerve is totally lacking. Data on genomic changes are available only on two benign and three malignant entities.

Schwannoma (or neurilemoma) represents a benign Schwann cell proliferation in which monosomy 22 has been reported. As the tumour suppressor gene *NF2* resides in 22q12, a close relationship with the neurofibromatosis type 2 (NF-2) syndrome in at least some cases may be postulated and, as a matter of fact, bilateral acoustic schwannomas are considered pathognomonic of the syndrome [65].

Perineurioma is a benign nerve sheath tumour distinct from hypertrophic neuropathy, which superficially bears a striking resemblance to meningioma. Immunohistochemical demonstration of EMA positivity along with S-100 protein and CD34 negativity plays a central part in the differential diagnosis with other neural or fibrohistiocytic lesions [39, 72]. Cytogenetically, abnormalities of chromosome 22 have been described [48].

Malignant peripheral nerve sheath tumours (MPNST) exist in two main forms: sporadic and associated with the NF-1 syndrome. Karyotypes are very complex but chromosomes 17q and 22q are very often involved [53].

Clear cell sarcoma represents a malignant lesion arising mostly around tendons and aponeuroses and is characterised by melanocytic differentiation; hence the denomination malignant melanoma of the soft parts. Clear cell sarcoma is now characterised cytogenetically and molecularly. The characteristic chromosome change is a t(12;22)(q13;q12) which leads to the fusion between the *EWS* (*EW*ing's *S*arcoma) gene on 22 and a transcription factor *ATF1* on 12q [110].

The Ewing's sarcoma/peripheral neuroectodermal tumour (ES/PNET) category represents a spectrum of round cell sarcomas exhibiting a partial neuroectodermal phenotype. These are characterised by expression of the CD99 antigen and their differential diagnosis includes all the other small round cell paediatric malignancies. The central karyotypic anomaly is a t(11;22) [3, 28, 105] with two other variants found in some cases of Ewing sarcoma: a t(21;22) [99] and a t(7;22) [52, 100], and a der(16)t(1;16) [77] as a secondary change. Molecularly the result of the t(11;22) is a fusion of the *EWS* gene with a truncated transcription factor FLI1 (*F*riend *L*eukemia virus *I*ntegration site *1*) on 11q24 belonging to the *ETS* (avian *E*rythroblastosis virus *T*ransforming *S*equence) family, resulting in an oncogenic conversion of the *EWS* gene, the normal function of which is still unknown. The gene contains an RNA-binding domain in the C-terminal portion and a region with transcriptional activating property in its N-terminal half, and it is ubiq-

uitously expressed. The other translocations occurring in less than 10% of cases also result in fusion between *EWS* and a member of the *ETS* family, *ERG* (*E*TS-*R*elated *G*ene) on 21, and *ETV1* (*E*TS *T*ranslocation *V*ariant *1*) on 7p22 [29].

Cartilage and bone tumours

Cytogenetic data concerning this group of tumours are still sparse. Yet, preliminary observations in soft parts chondroma indicate the involvement of chromosomes 6, 11 and 12q [18].

Among the malignant tumours the more closely characterised anomaly is represented by the t(9;22)(q22;q12) in extraskeletal myxoid chondrosarcoma (EMC) [96]. EMC has a tendency to indolent growth but shows a significant metastatic potential, especially to the lungs, in long-term follow-up observations. Main differential diagnoses are other myxoid sarcomas, such as myxoid liposarcoma and myxofibrosarcoma, and mixed tumours of adnexal origin, which may arise in the soft tissue [58]. Recently, in stark contrast to popular belief, it has been demonstrated that immunostaining for S-100 protein is negative in most cases [27]. The characteristic t(9;22) is found neither in other chondrosarcoma types nor in other lesions that have to be considered in the differential diagnosis. Molecularly the *EWS* gene on 22q this time fuses with TEC, the promotor region of *EWS*, causing oncogenic conversion of TEC, which is an orphan nuclear receptor [61].

Miscellaneous and unclassified soft tissue tumours

Among the benign tumours listed under this heading, which include several entities in which the line of differentiation is poorly understood or even unknown, cardiac myxomas may show a rearrangement of 12p12 [30].

Aggressive angiomyxoma, which is characterised by predominant (but not exclusive) occurrence in the vulva or pelvis of adult women, has shown involvement of the *MAR* region 12q13-q15 [54]. The malignant tumours include several entities that have been characterised. Alveolar soft tissue sarcoma, a somewhat enigmatic lesion in which skeletal muscle differentiation has been postulated on the basis of MyoD expression [44, 95], shows involvement of 17q25.

Extrarenal rhabdoid tumours (ERT), again, are a heterogeneous group of lesions, probably a phenotype rather than a true entity [84]. The morphological hallmarks of this rare lesion are large intracytoplasmic inclusions, which appear ultrastructurally as whorls of intermediate filaments, and macronucleoli. So far ERT, with the exception of central nervous system lesions, which exhibit monosomy of chromosome 22 [5], have failed to present consistent chromosome changes, and the rather minimal karyotypic anomalies observed contrast with the highly malignant behaviour of this tumour [33].

Intra-abdominal desmoplastic small round cell tumour (IADSRCT) is a highly malignant disease originally described as occurring predominantly intrabdominally, but a broader distribution has been demonstrated [10, 46, 85]. Morphologically, it is characterised by a polyphenotypic differentiation that includes expression of epithelial, neural and myoid markers. Because it usually involves mesothelium-lined sites, such as peritoneum, pleura and tunica vaginalis, a mesothelioblastic differentiation has been postulated [46, 85]. This tumour is characterised by a t(11;22)(p13;q12), which results in oncogenic activation of the *EWS* gene by the Wilms' tumour gene (*WT*): a unique example of a suppressor gene causing oncogenic conversion of another gene [47].

IADSRCT belongs to the family of small round cell tumours, along with PNET, neuroblastoma, alveolar rhabdomyosarcoma and some lymphomas. The characteristic genomic changes observed are a valuable diagnostic aid for the pathologist. In these cases, chromosome as well as molecular analysis [1, 34] can provide a quick and accurate diagnosis. Nonetheless, it must be stressed that as more sarcomas are karyotyped and analysed at the molecular level it is becoming evident that such genetic abnormalities are less specific than previously believed. Classic t(11;22) translocation has been recently reported in a bona fide alveolar rhabdomyosarcoma [104], indicating the need at least for evaluation of cytogenetic analysis with reference to morphology.

Interestingly, the occurrence of reciprocal translocations seems to represent a relatively common phenomenon in several subsets of soft tissue sarcomas (Table 2). The underlying molecular mechanisms need to be clarified and may serve as a general explanation of the mechanism of production of fusion proteins as well as of their role in molecular oncogenesis of sarcomas. In most examples the basic molecular aberration resulting from translocations is represented by the substitution of the RNA-binding domain (*EWS*, *FUS*) with a DNA-binding domain (*FLI*, *ERG*, *ETV*, *ATF1*, *CHOP*, *WT1*). The final result is that a protein involved in postranslational modifications tends to acquire transactivating properties, which confers the ability to interact with DNA and to stimulate the transcription of target genes. This appears to be true in a large variety of chimeric trancripts described so far, even if the actual functions of the normal genes involved remain to be fully elucidated in most circumstances.

It must also be noted that the *EWS* gene exhibit a high degree of "molecular promiscuity" as it plays a key role in a variety of sarcoma-specific translocations (ES/PNET, extraskeletal myxoid chondrosarcoma, myxoid liposarcoma, clear cell sarcoma, IADSRCT). The recent demonstration of loss of tumorigenicity in Ewing sarcoma cells expressing antisense RNA to the *EWS*-fusion transcript [81] indicates the therapeutic potential of the information provided by the genomic analysis of soft tissue tumours.

Conclusions

Recent cytogenetic and molecular genetic investigations in soft tissue tumours have provided us with new insights into the mechanisms underlying malignant transformation in mesenchymal tissues. Some soft tissue tumours now also have a distinct genetic identity represented by specific chromosome aberrations and by molecular changes related to these chromosome anomalies. Such genomic changes, when evaluated in context with morphology, represent an extremely valuable diagnostic aid to the pathologist. In the future, cytogenetics is bound to play an important diagnostic role in the case of lesions showing a borderline morphology and with the group of paediatric small round cell malignancies. Moreover, as for N-myc amplification in neuroblastoma, the possibility of a prognostic significance of genetic aberrations should be further explored.

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