Soft tissue tumors: an overview

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Identity

Note
Soft tissue tumours represent a heterogeneous and complex group of mesenchymal lesions that may show a broad range of differentiation. Histologic classification is based upon morphologic demonstration of a specific line of differentiation but, despite the extraordinary contribution of ancillary diagnostic techniques such as electron microscopy and immunohistochemistry, classification of mesenchymal neoplasms is still the subject of continuous debate. The true incidence of soft tissue tumors is nearly impossible to determine, especially for benign tumors, because many of these tumors are not biopsied. Soft tissue sarcomas compared with carcinomas and other neoplasms; do constitute fewer than 1% of all cancers. Their morphological appearance is kaleidoscopic and extremely varied. Hence, classification is often difficult and the subject of continuous debate among pathologists.

For the purpose of uniformity the new World Health Organization (WHO) Classification of Tumors of Soft Tissue and Bone will be followed. Dermatofibrosarcoma protuberance and giant cell fibroblastoma, which are fibroblastic neoplasms included in the WHO volume on Skin Tumors, are also included in this review.

The vast majority of so-called smooth muscle tumors arising in the gastrointestinal tract are in fact gastrointestinal stromal tumors, and these lesions are included in the WHO Classification of Tumors Pathology and Genetics of Tumors of the Digestive System. Benign uterine leiomyomas are included in the WHO Classification of Tumors Pathology and Genetics of Tumors of the Breast and female genital organs.

Informations and (review) references are provided for well-characterized cytogenetic/molecular tumors investigated in more than a single case.

Clinics and pathology

Disease

ADIPOCYTIC TUMORS

Cytogenetics

Lipoma: More than half the cases studied show an abnormal karyotype, mostly balanced translocation, as single abnormality. Three distinct clustering of breakpoints have been distinguished: 1) the major group involving 12q13-15; with several possible partners, of which 3q27-28 is a preferential one; 2) a deletion/translocation of 13q11-q22; 3) a rearrangement of 6p21-23. The target gene in 12q13-15 is a family member of the High Mobility Group (HMG) of protein, HMGA2 (a.k.a. HMGIC). In its preferential translocation region, 3q27-28, HMGA2 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. Another member of the same HMG family, HMG1A (a.k.a. HMG1Y) is the target in lipoma with 6p21-23 rearrangements.

Lipoblastoma: The characteristic cytogenetic feature is rearrangement of 8q11-13. This rearrangement is associated with promoter swapping, in which the PLAG1 promoter element is replaced by those of the hyaluronic acid synthase 2 (HAS2) or collagen (COL1A2) genes.

Angiolipoma: All cytogenetically investigated tumors but one have normal karyotypes.

Chondroid lipoma: A seemingly balanced t(11;16)(q13;p12-13) has been reported in two cases.

Spindle cell lipoma/Pleomorphic lipoma: Similar cytogenetic aberrations have been described in both entities: loss of material from the region 16q13-qter with or without monosomy 13, or partial loss of 13q.

Hibernoma: Involvement of 11q13 region has been described. However, FISH analysis demonstrated that these rearrangements are more complex than can be
Superficial fibromatoses: Near diploid karyotypes with simple numerical changes, particularly gain of chromosome 7 or 8, have been reported.

Desmoid-type fibromatoses: Trisomies for chromosome 8 and/or 20 have been described in some cases. Rearrangement of 5q is found in desmoid tumors from patients with familial polyposis. APC inactivation has been described, as well as beta-catenin activating mutations.

Extrapleural solitary fibrous tumor: No consistent abnormality has been detected. A possible involvement of 4q13 has been suggested.

Hemangiopericytoma: Disparate chromosome aberrations have been described. The 12q13-q15 and 19q13 have been the most frequent breakpoints described.

Inflammatory myofibroblastic tumor: Involvement of 2p23 occurs mainly or exclusively in children and young adults. Activation of the ALK receptor tyrosine kinase is accomplished by chromosomal fusion with TPM4 (19p13.1), TPM3 (1q22.23) and CLTCL2 (17q23) and is restricted to the myofibroblastic component of the tumors. The aberrations of ALK gene have been originally characterized as a component of the anaplastic large cell lymphoma NPM-ALK fusion oncprotein.

Infantile fibrosarcoma: A specific t(12;15)(p13;q26) is the hallmark of this tumor. Since the regions exchanged between chromosomes 12 and 15 are similar in size and banding characteristics, this translocation was overlooked in early reports, in which only numerical changes i.e. trisomies 11, 8, 17 and 20 were described. This translocation fuses the ETV6 (a.k.a. TEL) gene at 12p13 with the neurotrophin-3 receptor gene NTRK3 (a.k.a. TRKS) at 15q25. Notably, cellular congenital mesoblastic nephroma correlates with the presence of the same t(12;15) and with trisomy 11, but these findings are not seen in the classical congenital mesoblastic nephroma.

Adult fibrosarcoma: No consistent abnormality has been detected among the complex karyotypes published to date.

Myxofibrosarcoma: Highly complex karyotypes with extensive intratumoral heterogeneity have been reported. No consistent aberration has emerged.

Low grade fibromyxoid sarcoma: No consistent abnormality has been detected.

Sclerosing epithelioid fibrosarcoma: No consistent abnormality has been detected among the 3 tumors so far reported.

Dermatofibrosarcoma protuberans / Giant cell fibroblastoma: The t(17;22)(q22;q13) and, more often a supernumerary ring chromosome derived from this translocation, are the characteristic chromosome aberrations in these entities. In some rings additional segments from other chromosomes could be detected by conventional G-banding and affect the seemingly normal chromosome 11.

Atypical lipomatous tumor/Well-differentiated liposarcoma: Supernumerary ring or and giant marker chromosomes have been observed mostly as the sole chromosome aberration. Cells containing ring and/or giant markers varying in size or number can be observed in the same tumor sample. Telomeric associations are frequently seen. Molecular cytogenetic techniques indicate that both ring and giant marker chromosomes are composed of interspersed amplified sequences consistently originating from the 12q14-15 region. The most consistently amplified gene is MDM2, usually accompanied by amplification of neighbouring genes, such as SAS, CDK4 and HMGA2 (a.k.a. HMGIC). Additional chromosomal regions have been shown to be coamplified with 12q14-15.

Dedifferentiated liposarcoma: Partial or complete loss of chromosome 1 were particularly noted.

Involvement of the neighbour region of 11q12 has been observed in two cases.

Desmoplastic fibroblastoma: t(2;11)(q31-32;q12) has been reported.

Mammary-type fibroblastoma: The same region of 11q12 has been observed in two cases.

Fibroma of the tendon sheath: Aberrations of the short arm of chromosome 1 were usually accompanied by amplification of the neighbour region, such as SAS, CDK4 and HMGA2 (a.k.a. HMGIC). Additional chromosomal regions have been shown to be coamplified with 12q14-15.

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identified. Both rings and translocations contain a fusion of two genes COL1A1 (17q21-22) and PDGFB (22q13).

Disease
SO-CALLED FIBROHISTIOCYTIC TUMORS
Cytogenetics
Giant cell tumor of tendon sheath: The region most frequently involved in structural rearrangements is 1p11-13. Chromosome 2q35-36 region is the most common translocation partner described. Other chromosome aberrations observed include involvement of 16q24 and trisomies 5 and/or 7. A breakpoint clustering to the sequences corresponding to YAC probes 914F6 and 88F12, located in 1p3.2, has been identified.
Diffuse-type giant cell tumors: The structural and numerical abnormalities described are similar to those observed in (localized form) giant cell tumor of the tendon sheath; however trisomies for chromosomes 5 and 7 are more frequently encountered in the diffuse form of the tumor.
 Plexiform fibrohistiocytic tumor: No consistent abnormality has been detected among the 2 tumors so far reported.
Pleomorphic malignant fibrous histiocytoma: In general the karyotypes tend to be the triploi-tetraploid range, with complex chromosome aberrations, numerous marker chromosomes and with extensive intratumoral heterogeneity. No common chromosome aberrations emerge, but telomeric associations, ring chromosomes and dicentric chromosomes are frequently encountered.

Disease
SMOOTH MUSCLE TUMORS
Cytogenetics
Angioleiomyoma: No consistent abnormality has been reported from the 4 tumors investigated to date.
 Leiomyosarcoma: Most karyotypes are complex and no consistent aberrations have been reported.

Disease
PERICYTIC (PERIVASCULAR) TUMORS
Cytogenetics
No cytogenetic investigations have been reported in this category of soft tissue tumors.

Disease
SKELETAL MUSCLE TUMORS
Cytogenetics
Embryonal rhabdomyosarcoma: Complex karyotype are generally reported, including extra copies of chromosomes 2, 8 and 13, and rearrangements of chromosome 1. However, loss of heterozygosity of 11p15 region is found in most of these tumors. Imprted tumor supressor genes i.e. IGF2, H19and CDKN1Chave been suggested as the the mechanism of tumorigenesis in these tumors.
Alveolar rhabdomyosarcoma: A specific t(2;13)(q35;q14) characterizes this type of rhabdomyosarcoma. The genes involved are the PAX3 gene on 2q35 and the FKHR gene on 13q14. A variant translocation has been described, t(1;13)(p36;q14), which fuses PAX7gene on 1p36 with FKHR. Tumors with PAX7-FKHR fusion transcript show a predeliciton for younger patients, appear in the extremities and have a better prognosis.
Pleomorphic rhabdomyosarcoma: Highly complex karyotypes have been reported.

Disease
VASCULAR TUMORS
Cytogenetics
Kaposi sarcoma: No consistent abnormality has been detected neither cell lines or primary tumors.
Epithelioid hemangioendothelioma: An identical t(1;3)(p36;.3q25) has been reported in 2 cases.
Angiosarcoma of the soft tissue: All reported tumors, but one, have complex cytogenetic aberrations without consistent recurring chromosome aberration. However there are some recurrent aberrations among angiosarcomas arising in the same location.

Disease
CHONDRO-OSSEOUS TUMORS
Cytogenetics
Soft tissue chondroma: No consistent abnormality has been detected among the 4 tumors studied to date.
Extraskeletal osteosarcoma: No consistent abnormality has been detected among the 3 tumors studied to date.

Disease
TUMORS OF UNCERTAIN DIFFERENTIATION
Cytogenetics
Intramuscular myxoma: One single case reported a hyperdiploid clone with trisomy 18.
Juxta-articular myxoma: One single case reported two unrelated abnormal clones.
Deep "aggressive" angiomyxoma: Abnormalities of chromosome 12 have been reported. The most frequently rearranged chromosome region is 12q13-15 and HMGA2 is the target gene.
Angiomatoid fibrous histicytoma: One case exhibited a complex translocation involving chromosomes 2,17,12, and 16. Further molecular investigation revealed that the FUS (also known as TLS) gene, mapping to chromosome band 16p11, was fused with the ATF1gene, located in band 12q13. The translocation thus generates a chimeric FUS/ATF1 protein, similar to the EWS/ATF1 chimeric protein
seen in clear cell sarcomas with t(12;22) (q13;q12). Identical fusion of FUS and ATF1 genes were reported in a second case.

**Ossifying fibromyxoid tumor:** One single case has been reported.

**Mixed tumor/Myoepithelioma/Parachordoma:** No consistent abnormality has been detected among the 3 tumors studied to date.

**Synovial sarcoma:** A specific t(X;18)((p11.2;q11.2) characterizes both mono-phasic and biphasic morphologic variants. The vast majority of primary tumors show a near-diploid karyotype, while the recurring and metastasis lesions carry additional chromosome aberrations. Involvement of a third (or more) chromosome has been reported. The t(X;18) results in two gene fusions in which the SYT gene at 1q12 joins either of two closely related genes at Xp11.2, designated SSX1 or SSX2. The monophasic variant exhibits SYT-SSX1 or SYT-SSX2 transcripts and the majority of the biphasic one SSX1. The formation of the respective fusions is generally mutually exclusive and remains constant during the course of the disease. Moreover the SYT-SSX2 fusion is considered a strongly positive prognostic factor for overall survival because it is associated with a lower prevalence of metastatic disease at diagnosis.

**Epithelioid sarcoma:** No consistent abnormalities have been detected. A possible role of 8q has been suggested.

**Alveolar soft part sarcoma:** A specific chromosome aberration, der (17)t(X;17)(p11;q25), is the hallmark of this sarcoma. This translocation fuses the TFE3 transcription factor gene at Xp11.2 to a novel gene at 1q25, designated as ASPL (a.k.a ASP-SCR1 or RCC17). Of interest, the balanced t(X;17)(p11.2;q25) has been also described in renal tumors of young people. An identical ASPL-TFE3 fusion transcript, seen in alveolar soft part sarcoma, has been detected, as has the reciprocal fusion transcript TFE3-ASPL.

**Ewing sarcoma/Primitive neuroectodermal tumor:** The t(11;22)(q24;q12) was the first specific change to characterize this entity, though variant translocations have been also described. The t(11;22) results in fusion of the EWS gene at 22q12, or with RBP56 gene at 17q11 or with TCF12 gene at 15q21.

**Desmoplastic small round cell tumor:** A specific chromosome abnormality, (t11;22)(p13;q12) characterizes this entity, though variant translocations have been also described. The t(11;22) results in the fusions of two chromosomal region previously implicated in other malignant tumors: the Wilms tumor gene (WT1) localized to 11p13 and the Ewing sarcoma (EWS) gene localized to 22q12.

**Extrarenal rhabdoid tumor:** Abnormalities of 22q11.2, as translocations and deletions, have been detected in these distinct tumors arising in any part of the human body. Mutations and homozygous deletions of the SMAR-CB1 (a.k.a. hSNF5 or INI1) gene have been detected.

**PEComas (perivascular epithelioid cell tumors):** One single case has been reported.

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