Soft tissue tumors: an overview

Paola Dal Cin
Brigham and Women’s Hospital, 75 Francis Street, Boston, MA 02115, USA (PD)

Published in Atlas Database: July 2013
Online updated version: http://AtlasGeneticsOncology.org/Tumors/softissuTumID5042.html
DOI: 10.4267/2042/52079

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© 2014 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Abstract: Review on soft tissue tumors with data on clinics, and the genes involved.

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, constitute fewer than 1% of all cancers. Their morphological appearance is kaleidoscopic and varies. 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 published in 2013 will be followed. A few new categories have been officially included in the Soft Tissue Tumour section: giant cell fibroblastoma, dermatofibrosarcoma protuberans, gastrointestinal stromal tumours and nerves sheath tumours. Undifferentiated/unclassified sarcomas are a new entity in this new edition. Ewing sarcoma and extraskeletal mesenchymal chondrosarcoma, originally described in the Bone section is also included in this review. Benign uterine leiomyomas and endometrial stromal sarcoma are still included in the WHO Classification of Tumors Pathology and Genetics of Tumours of the Breast and Female Genital Organs. Moreover, a few new cytogenetic-molecular and histological correlations have been enclosed.

Informations and (review) references are provided for well-characterized cytogenetic/molecular tumors investigated in more than a single case. For data regarding single case reported, the reader is referred to http://cgap.nci.nih.gov/Chromosomes/Mitelman; 2013.

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 12q14.3, HMGA2 (HMGIC) is a family member of the High Mobility Group (HMG) of protein. The most common gene fusion is HMGA2-LPP resulting from a t(3;12)(q27-28;q14.3). Other partners genes include: CXCR7 (2q37.3), EBF1 (5q33.3), NFIB (9p22.3), LHFP (13q13.3) and PPAP2 (1p32). Lipoma with 13q- show a minimal deleted region of 3.4 Mb, where only the C13orf11 is expressed in significant lower level compared with lipomas without 13q deletion. In lipoma with 6p21-23 rearrangement, the breaks occur adjacent to the coding sequences of HMGA1 (HMG1Y), another member of the same HMG family.
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, at 8q24.3 and 7q21.3, respectively. The most common numerical is one or more extra copies of chromosome 8, with or without 8q11-13 rearrangement.

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

Chondroid lipoma. C11orf95 and MLK2 genes at 11q13 and 16p13.3, respectively, are the genes involved in the t(11;16)(q13;p12-13).

Spindle cell lipoma/Pleomorphic lipoma. Similar cytogenetic aberrations have been described in both entities. The most frequent losses are -13/13q-, followed by 16q22-qter, 6q14-21, 10p and 17p, and 2q21-. Hibernoma. Involvement of 11q13 region has been described, with several translocation region partners, of which 9q34 and 14q11 are the most recurrent ones. However, FISH analysis demonstrated that these rearrangements are more complex than can be detected by conventional G-banding and interstitial deletions affect the seemingly normal chromosome 11. This deletion clusters to a 3 Mb region in 11q13 of the 132 genes in this 3 Mb region. Several genes showed significant lower expression including MEN1, AIP, EHD1 and CDK2AP2. High expression was also seen with PPARA, PPARG, PPARGC1A and particularly EHD1 and CDK2AP2. High expression was also seen with PPARA, PPARG, PPARGC1A and particularly EHD1 and CDK2AP2. High expression was also seen with PPARA, PPARG, PPARGC1A and particularly EHD1 and CDK2AP2. High expression was also seen with PPARA, PPARG, PPARGC1A and particularly EHD1 and CDK2AP2. High expression was also seen with PPARA, PPARG, PPARGC1A and particularly EHD1 and CDK2AP2. High expression was also seen with PPARA, PPARG, PPARGC1A and particularly EHD1 and CDK2AP2.

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 neighboring genes, such as CDK4, HMGA2, YEATS4, CPM, and FRS2. Additional chromosomal regions have shown to be co-amplified with 12q14-15, and with 1q21-q25 being the most frequent region. These ring and giant marker chromosomes do not contain ana-satellite sequences, but have "neocentromere".

Dedifferentiated liposarcoma. Cytogenetic anomalies similar to those seen in atypical lipomatous tumors have been reported. Moreover, co-amplification involving mainly 1p32 and 6q23, which include JUN and its active kinases ASK1 as target genes, has been demonstrated.

Myxoid liposarcoma. The characteristic cytogenetic feature is t(12;16)(q13;p11), leading to the fusion of two genes DDIT3 (CHOP) and FUS (TLS). A rare variant translocation has been also described, t(12;22)(q13;q12), in which DDIT3 is fused with EWSR1. The absence of FUS/DDIT3 fusion in other morphologic mimics, such as myxoid well differentiated liposarcomas of the retroperitoneum and myxofibrosarcoma, has been demonstrated.

Pleomorphic liposarcoma. High chromosome numbers with complex structural rearrangements have been often described. The absence of amplification of 12q14-15 can help to distinguish pleomorphic liposarcoma from dedifferentiated liposarcoma.

**Disease**

Fibroblastic/Myofibroblastic tumors

**Cytogenetics**

Nodular fasciitis. The overexpression of USP6 gene in this lesion prompted to the identification of a USP6-MYH9 gene fusion, as consequence of a cryptic t(17;22)(p13.3;q12.3).

Angiofibroma of the soft tissue. Although this benign lesion was not included in the WHO 2013, a t(5;8)(p15;q13) associated with AHRR-NCOA2 gene fusion is the hallmark of this lesion.

Proliferative fasciitis and proliferative myositis. For each of these entities, trisomy 2 has been reported in a single case.

Elastofibroma. A significant chromosomal instability has been reported. Aberrations of the short arm of chromosome 1 were particularly noted.

Juvenile hyaline fibromatosis. This lesion is caused by the inactivating mutation in the ANTXR2 gene encoding capillary morphogenesis protein 2, at 4q21.

Fibroma of the tendon sheath. A single case with t(2;11)(q31-32;q12) has been reported. This translocation is apparently identical to the one reported on desmoplastic fibroblastoma.

Desmoplastic fibroblastoma. A t(2;11)(q31-32;q12) or a 3-way variant has been observed. Deregulated expression of FOSL1 gene has been proposed as the functional outcome of the 11q12 rearrangement.

Mammary-type fibroblastoma. Partial monosomy 13q with or without partial monosomy 16q have been reported, similar to those described for spindle cell lipoma, and cellular angiofibroma, supporting a pathogenic link among these entities.

Cellular angiofibroma. One single case reported with loss of 13 and 16, Interphase FISH showing deletion of RB1 and FOXO1 support this finding.

Palmar/plantar fibromatoses. Near-diploid karyotype 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 reported in tumor arising in the setting of Gardner-type FAP. Mutations in the β-catenin...
(CTNNB1) have been detected in 85% of sporadic lesions.

**Giant cell fibroblastoma.** Only few cases have been analyzed by karyotyping, and either t(17;22)(q22;q13) or unbalanced t(17;22), has been observed in pediatric cases. This chromosome rearrangement is associated with COL1A1-PDGFB chimeric gene. Similar gene rearrangement has been identified in dermatofibrosarcoma protubersans.

**Dermatofibrosarcoma protuberans.** A supernumerary ring/chromosome derived from a t(17;22)(q22;q13) is characteristic chromosome aberrations. This ring chromosome contains the centromeric region of chromosome 22, more than one copy of COL1A1-PDGFB gene fusion, and sometime, additional segments from other chromosomes. Clinical studies have shown a high response rate to imatinib therapy in both locally advanced and metastatic tumors, as imatinib blocks PDGFRB signaling.

**Extrapleural solitary fibrous tumor.** After the publication of WHO13, a NAB2-STAT6 gene fusion was identified by next generation sequencing and has not been encountered in other soft-tissue tumors. This fusion result by a paracentric inversion on the 12q13 region, where both NAB2 and STAT6 are genes closely adjacently located, overlapping 58 base pairs. Therefore this inversion is undetectable by standard G-banding karyotyping, and only a minor fraction of the fusion-positive cases can be identified by FISH analysis.

**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 translocation to a wide variety of partner genes, with TPM4 (19p13.1), TPM3 (1q22.23), CLTCL2 (17q23), RANBP2 (2q13), ATIC (2q24), CARS (11p15) and SEC31L1 (4q21), being the most frequent. Of interest, the RANBP2-ALK gene fusion has an aggressive clinical course and shows a ALK immunostaining in a nuclear membrane pattern. Some of these ALK fusion genes have been observed in anaplastic large cell lymphoma and in diffuse large B-cell lymphoma. Moreover, ALK rearrangement has been also reported in a subgroup of non-small lung cancer, kidney tumors, esophageal squamous cell carcinoma.

A fraction of all these cancer types shares activated ALK as the essential growth driver and such tumors can be targeted for treatment with ALK inhibitors e.g. Crizotinib.

**Malignant fibrous histiocytoma.** Most of these lesions share a balanced or unbalanced t(1;10)(p22;q24-25).

The breakpoints on this translocation are TGFBR3 in 1p22 and MGEA5 in 10q24. However, no chimeric fusion transcript is detectable because these two genes are transcribed in opposite directions.

Over-expression of FGF8 on 10q was identified by microarray analysis, suggesting that this translocation may alter gene transcription away from the breakpoint. The loss of material of the chromosome region 3p is associated with amplification of 3p11.1-12.1, containing VGLL3 gene. Similar t(1;10) abnormality has been also observed in hemosiderotic fibrolipomatous tumour.

**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 (TEL) gene at 12p13 with the neurotrophin-3 receptor gene NTRK3 (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. The same t(12;15) has been reported in myeloid leukemia, secretory breast carcinoma, and mammary-type secretory carcinoma and salivary glands.

**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.** A t(7;16)(q33;p11) is present in approximately two third of the cases, and a 25% of the cases show a supernumerary ring chromosome.

Both aberrations result by a FUS-CREB3L2 gene fusion. A rare variant t(11;16)(p11;p11) leading to a FUS-CREB3L1 gene fusion have been reported.

**Sclerosing epithelioid fibrosarcoma.** FUS rearrangement is rarely detected in pure sclerotic epithelial fibrosarcoma, but it has been detected in low-grade-fibromyxoid sarcoma with sclerosing epithelial fibrosarcoma-like loci.

**Disease**

**So-called fibrohistiocytic tumors**

**Cytogenetics**

Tenesynovial giant cell tumour, localized type. The most frequent translocation is the t(1;2)(p13;q35) and is associated with a CSF1-COL6A3 gene fusion, resulting in an over-expression of CSF1 in the neoplastic cells. No other CSF1 gene partners have yet been identified. The biologic evidence of a central role for CSF1 in the pathogenesis of these lesions is further supported by clinical experience, in which they responded therapeutically to imatinib. Involvement of 16q24 and trisomies 5 and/or 7 can also be observed.
Tenosynovial giant cell tumour, diffuse-type. The structural and numerical abnormalities described are similar to those observed in localized form, however trisomies for chromosomes 5 and 7 are more frequently encountered in the diffuse form of the tumor.

Deep benign fibrous histiocytoma. A t(16;17)(p13.3;q21.3) was reported in a single case.

Plexiform fibrohistiocytic tumor. No consistent abnormality has been detected among the 3 tumors so far reported.

Giant cell tumors of the soft tissue. Multiple telomeric associations were reported in single case, like giant cell tumor of the bone.

Disease
Smooth muscle tumors

Cytogenetics

Leiomyosarcoma. Most karyotypes are complex and no consistent aberrations have been reported. However, some common gains or losses of genetic material have been detected by cytogenetic and comparative genomic hybridization (CGH) studies some aberrations may be more related to the site of origin than to the morphologic features of the tumors. Involvement of TP53, FANCA, RB, PTEN, MYOCD and ROR2 have been reported.

Disease
Pericytic (perivascular) tumors

Cytogenetics

Myopericytoma, including myofibroma. A small group of tumors considered to fall within the myopericytic category exhibits a t(7;12)(p22;q13) that results in the fusion of ACTB and GLI1 genes.

Angioleiomyoma. Simple karyotypes with non-random structural aberration have been so far reported. Genomic array analysis showed that 22q11.2 is most common lost region, while the most gain is Xq arm.

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. Imprinted tumor suppressor genes i.e. IGF2, H19 and CDKN1C and HOTS have been suggested as the mechanism of tumorigenesis in these tumors. Several other individual genes have been also implicated in a subset of tumor e.g. RB1, TP53, RAS, GLI1, FGFR4, PIK3CA, CTNNB1, ALK.

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 FOXO1 gene on 13q14. A variant translocation has been described, t(1;13)(p36;q14), which fuses PAX7 gene on 1p36 with FOXO1. Tumors with PAX7-FOXO1 gene fusion transcript show a predilection for younger patients, appear in the extremities and have a better prognosis. An interesting distinctive feature of ARMS with the PAX7-FOXO1 is that the fusion gene is often duplicated or amplified. However, 20% of cases have neither t(2;13) nor t(1;13). Some of these cases have variant translocations involving either PAX or FOXO1 (e.g., PAX-NCOA1, PAX3-AFX, FOXO1/FGFR1).

Pleomorphic rhabdomyosarcoma. Highly complex karyotypes have been reported.

Spindle cell/sclerosing rhabdomyosarcoma. PAC2/PAX7-FOXO1 fusions are virtually always absent. Pediatric cases of spindle cell rhabdomyosarcoma have recently been found to contain fusions of the NCOA2 gene at 8q13, with SRF or TEAD1. Therefore, this new correlation is not included in the WHO13. Adult spindle cell rhabdomyosarcoma do not appear to contain NCOA2 rearrangement.

Disease
Vascular tumors

Cytogenetics

Kaposi sarcoma. No clinically relevant genetic changes have been reported.

Pseudomyogenic hemangioendothelioma. A single case with a t(7;19)(q22;q13).

Epithelioid hemangioendothelioma. A t(1;3)(p36.3;q25) has been associated with a rearrangement between CAMTA1 gene (at 1p36.3) and WWTR1 gene (at 3q25). This rearrangement has not been detected in any of the morphological mimics of epithelioid hemangioendothelioma, such as hemangioendothelioma, epithelioid angiosarcoma, or epithelioid sarcoma-like hemangioendothelioma. More recently, and therefore not reported in the WHO13, a small subset of EHE, with somewhat different morphology has been found to harbor TEF3 rearrangement, instead of the WWTR1-CAMTA1 gene fusion.

Angiosarcoma of the soft tissue. High level of MYC 8q24 amplification is a consistent finding in radiation - induced and lymphoedema -associated angiosarcoma. Co-amplification of FLT4 (5q35) can be also observed in 25% of secondary angiosarcoma.

Disease
Chondro-osseous tumors

Cytogenetics

Soft tissue chondroma. Three subgroups of chromosome rearrangements were observed so far: 1) rearrangement of 12q13-15, 2) trisomy 5 and 3) loss 11q21-qter. Different HMG2A involvements were reported on those chondromas with 12q13-q15
Disease

Nerve sheath tumors

Cytogenetics

Schwannoma (including variants). Monosomy 22/22q- is the most common chromosome aberration in classic and cellular schwannoma. Both NF2 and SMARCB1 (hSNF5, INI1) have been implicated on the tumorigenesis, as "four-hit" or "three-hit". Trisomy 17 has been observed in plexiform cellular variants.

Melanotic schwannoma. Amplification/deletion of 2p16 region was demonstrated in 80% of lesions in patient with/without Carney complex.

Neurofibroma (including variants). Inactivation of both copies of NF1 at 17q11.2 can occur in individuals with or without neurofibromatosis type I. 9p deletion containing CDKN2A, CDKN2B and MTAP has been frequently detected in localized intraneural and plexiform neurofibromas.

Perineurioma. Monosomy 22/22q- is observed in these lesions targeting NF2 tumor suppressor gene. Additional 10q abnormalities have been identified in sclerosing variant.

Malignant peripheral nerve sheath tumour. Complex karyotypes have been reported with numerical and structural rearrangements including: 1p, 9p21 (CDKN2A), 10p, 11p, 13q14 (RB1), 17p13 (TP53), 17q11.2 (NF1), 22q12.2 (NF2) as the most frequent chromosomal losses, and 7p, 7q, 8q, and 5q the most frequent chromosomal gains. These tumours are associated with bi-allelic inactivation of NF1, but their development requires additional mutations in CDKN2A or TP53, both in familial and sporadic cases.

Tumors of uncertain differentiation

Cytogenetics

Intramuscular myxoma. No consistent aberrations were observed in the 5 cases so far karyotyped. However, point mutations of GNAS are common in these lesions.

Juxta-articular myxoma. One single case reported two unrelated abnormal clones. No GNAS mutations have been detected so far.

Deep 'aggressive' angiomyxoma. Abnormalities of chromosome 12 have been reported. The most frequently rearranged chromosome region is 12q13-15 and HMGAA2 is the target gene either by generation of a fusion transcript or alteration affecting the 3' telomeric untranslated region.

Angiomatoid fibrous histiocytoma. Three different translocations have been described: 1) t(12;16)(q13;p11) associated with ATF1-FUS fusion, 2) t(12;22)(q13;q12) associated with EWSR1-ATF1 gene fusion and 3) t(2;22)(q34;q12) associated with EWSR1-CREB1 gene fusion. Both t(12;22) and t(2;22) have also been reported in clear cell sarcoma.

Atlas Genet Cytogenet Oncol Haematol. 2014; 18(1)
Ossifying fibromyxoid tumor. The PHF1 gene at 6p21, previously shown to be involved in some endometrial stromal tumors, is also recurrently rearranged in ossifying fibromyxoid lesions classified as typical or atypical. Loss of chromosome 22 has been observed in malignant lesions.

Myoepithelioma/Myoepithelial carcinoma/Mixed tumour. EWSR1 (22q12) rearrangement have been reported in approximately 50% of cases. The t(6;22)(p21;q12) involving EWSR1 and POU5F1 genes have been identified in a subset of deep seated tumors of extremities, in children or young adults with distinct clear cell morphology. The t(1;22)(q23;q12) involving EWSR1 and PBX1 genes has been identified in a subset of tumors with a deceptively bland appearance, composed mainly of spindle cells embedded in a fibrotic stroma, resembling in areas desmoid-type fibromatosis. A third translocation, t(19;22)(q13;q12) associated with EWSR1 and ZNF444 genes has been also identified in less than 2% of the cases, without any specific morphology. PLAG1 rearrangement was identified in a subset of EWSR1 negative myoepithelial tumors, more often benign, superficially located, and show ductal differentiation supporting a common pathogenesis with their salivary gland counterparts.

Hemosiderotic fibrolipomatous tumour. Similar t(1;10)(p22;q24-25) and chromosome aberrations involving chromosome 3 with amplification of 3p11.1-12 have been observed in myxoinflammatory fibroblastic sarcoma.

Synovial sarcoma. A specific t(X;18)(p11.2;q11.2) characterizes both monophasic 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 18q11 or with TCF12 gene at 15q21. A specific chromosome aberration, t(11;22)(q24;q12) was the first specific change to be defined in sarcoma. Secondary changes i.e. +8, +12 and der(16)(t1;16) were also frequently reported. The t(11;22) is associated with EWSR1-FLI1 fusion gene. However rare variant translocation have been reported, where the EWSR1 gene fuses with different ETS-family gene partners such as the ERG gene at 21q22, the ETV1 at 7p22, E1AF at 17q12, FEV at 2q3. In addition cases with FUS-ERG or FUS-FEV gene fusions have been also rarely described. Variability in molecular transcripts has been reported, but the initial reported survival differences are no longer apparent with current treatment protocols. Secondary changes i.e. +8, +12, der(16)(t1;16), +20 were also frequently reported.

Clear cell sarcoma of the soft tissue. The t(12;22)(q13;q12) is the more frequent cytogenetic change in this type of sarcoma and it is associated with EWSR1 (22q12) and ATF1 (12q13) genes. A specific chromosome aberration has been detected almost exclusively in tumors of gastrointestinal (GI) tract. However, the clear cell sarcomas in GI tract with either EWSR1-ATF1 or EWSR1-CREB1 lack melanocytic markers, in contrast to the EWSR1-ATF1 soft tissue clear cell sarcoma. The spectrum of tumors with EWSR1-ATF1 and EWSR1-CREB1 gene fusions has further expanded to include angiomatoid fibrous histiocytoma, hyalinizing clear cell carcinoma of the salivary gland, and primary pulmonary myxoid sarcoma.

Extraskelatal myxoid chondrosarcoma. A specific chromosomal abnormality, t(9;22)(q22;q12) characterizes this entity, though variant translocations have been also described. Variant translocations have been also reported: t(9;17)(q22;q11) and t(9;15)(q22;q21). All three translocations result in fusion of the NR4A3 (CHN, TEC) gene at 9q22 with the EWSR1 gene at 22q12, or with RBP56 gene at 17q11 or with TCF12 gene at 15q21.

Desmoplastic small round cell tumor. A specific chromosomal abnormality, t(11;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 (EWSR1) gene localized to 22q12.

Extranodal rhabdoid tumor. Abnormalities of 22q11.2, as translocations and deletions, have been described in these distinct tumors arising in any part of the human body. Mutations and homozygous deletions of the SMARCB1 gene have been detected.

PEComas. These tumors are seen in the context of the Tuberous Sclerosis Complex syndrome caused by germline mutations in either TSC1 (OMIM: 191100) or TSC2 (OMIM: 613254). Sporadic PEComas often show complex karyotypes with loss of TSC2.
A smaller subset of PEComas, approximately 10%, harbors TFE3 fusions, but without TSC2 loss.

**Intimal sarcoma.** Gain and amplification of 12q12-15, containing CDK4, TSPAN31, MDM2, GLI, and of 4q21 containing PDGFRα and KIT (CD117) are the most constant genetic aberrations detected by CGH. EGFR amplification/polysomy has been also detected. Very frequently co-amplification or gains of PDGFRα, EGFR and MDM2 occur.

**Disease**

**Undifferentiated/unclassified sarcomas**

**Cytogenetics**

Undifferentiated round cell and spindle cell sarcomas. Two different entities have been reported: 1) sarcomas with fusions of EWSR1 to non-ETS family transcription factor genes such as SP3, PATZ1, SMARCAS, POU5F1, NFATC2, often as single case; 2) Ewing sarcoma-like tumours defined as “EWSR1-fusion negative”. Two distinct genetic events have been so far reported, both arising in children and young adults: a) either CIC-DUX4 gene fusion, resulting from t(4;19)(q35;q13) or t(10;19)(q26.3;q13) or b) a BCOR-CCNB3 gene fusion, as the result of a paracentric inversion on the short arm (p) of the X-chromosome.

**Undifferentiated pleomorphic sarcoma.** High-grade pleomorphic sarcomas, including many tumors formerly called MFH, generally have complex and nonindistinctive karyotype and may represent the most undifferentiated state of other sarcomas. Those undifferentiated sarcomas with 12q12-15 amplification including MDM2 and CDK4, are now classified as dedifferentiated liposarcoma.

**References**


Sjögren H, Wedell B, Meis-Kindblom JM, Kindblom LG, Stenman G. Fusion of the NH2-terminal domain of the basic helix-loop-helix protein TCF12 to TEC in extraskeletal myxoid chondrosarcoma with translocation t(9;15)(q22;q21). Cancer Res. 2000 Dec 15;60(24):6832-5

Waters BL, Panagopoulos I, Allen EF. Genetic characterization of angiomatoid fibrous histiocytoma identifies fusion of the FUS and ATF1 genes induced by a chromosomal translocation involving bands 12q13 and 16p11. Cancer Genet Cytogenet. 2000 Sep;121(2):109-16


Sjögren H, Wedell B, Meis-Kindblom JM, Kindblom LG, Stenman G. Fusion of the NH2-terminal domain of the basic helix-loop-helix protein TCF12 to TEC in extraskeletal myxoid chondrosarcoma with translocation t(9;15)(q22;q21). Cancer Res. 2000 Dec 15;60(24):6832-5
chromosome 1, is characteristic of elastofibroma. Cancer Genet Cytogenet. 2001 Apr;126(1):68-72


Parham DM. Pathologic classification of rhabdomyosarcomas and correlations with molecular studies. Mod Pathol. 2001 May;14(5):506-14


Raddaoui E, Donner LR, Panagopoulos I. Fusion of the FUS and ATM1 genes in a large, deep-seated angiomatoid fibrous histiocytoma. Diagn Mol Pathol. 2002 Sep;11(3):157-62


Hallor KH, Sciot R, Staaf J, Heidenblad M, Rydhholm A, Bauer HC, Aström K, Domanski HA, Meis JM, Kindblom LG, Panagopoulos I, Mandal N, Mertens F. Recurrent fusions t(1;10) and amplification of 3p11-12, in myxoinflammatory fibroblastic sarcoma, haemosiderotic fibrolipomatous tumour, and morphologically similar lesions. J Pathol. 2009 Apr;217(5):716-27


Antonescu CR, Zhang L, Chang NE, Pawel BR, Travis W, Katabi N, Edelmann M, Rosenberg AE, Nielsen GP, Dal Cin P, Fletcher CD. EWSR1-POU5F1 fusion in soft tissue myoepitheliomas. A molecular analysis of sixty-six cases, including soft tissue, bone, and visceral lesions, showing common involvement of the EWSR1 gene. Genes Chromosomes Cancer. 2010 Dec;49(12):1114-24


Huang D, Sunmegi J, Streblow R, Frayer RW, Dal Cin P, Rosenberg A, Meloni-Ehrig A, Bridge JA. Recurrent t(2;2) and t(2;8) translocations in rhabdomyosarcoma without the canonical PAX-FoxO1 fusion tPAKX to members of the nuclear receptor transcriptional coactivator family. Genes Chromosomes Cancer. 2010 Mar;49(3):224-36


This article should be referenced as such: