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REVIEW AND PERSPECTIVE

Soft tissue sarcomas with non-EWS translocations: molecular genetic features and pathologic and clinical correlations

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Abstract Many soft tissue sarcoma subtypes have consistent chromosomal translocations with novel fusion genes, which result in disordered cellular function. The microscopic appearances, immunophenotype and behaviour of such tumours relate to the genetic events to a variable extent. This paper reviews the molecular pathology and related morphological and clinical features of sarcomas with non-EWS translocations. These include synovial sarcoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, dermatofibrosarcoma protuberans, low-grade fibromyxoid sarcoma, infantile fibrosarcoma and inflammatory myofibroblastic tumour.

Keywords Translocation · Soft tissue sarcoma · Molecular genetics

Introduction

Increasing numbers of soft tissue sarcoma subtypes are found to have consistent chromosomal translocations with formation of fusion genes whose products and interactions affect cell proliferation, growth and survival. The initiating factors for most gene fusions are unknown [1]. However, the genetic rearrangements and fusion gene products are now routinely demonstrable in fixed tissue using fluorescence in situ (FISH) and reverse transcription polymerase chain reaction (RT-PCR) techniques, and the patterns of gene activation can be displayed by gene expression profiling. These developments have led to improved diagnosis and to an increasing influence of genetic findings on clinical management of these rare tumours.

Sarcomas with non-EWS translocations are spindle, polygonal or small round cell tumours with varying behaviour, which mostly occur in children or young adults. They include synovial sarcoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, dermatofibrosarcoma protuberans, low-grade fibromyxoid sarcoma, infantile fibrosarcoma and inflammatory myofibroblastic tumour. This paper reviews the molecular genetic findings in these sarcoma types and their relationship with morphological, immunohistochemical and clinical features.

Synovial sarcoma

Synovial sarcoma does not arise from or differentiate towards synovium and the name is a historical error [2]. This tumour is extremely rare within joints [3–5] and generally arises in periarticular connective tissue and most commonly around the knee. Identification of the t(X;18) by cytogenetic or molecular means, however, has confirmed that synovial sarcoma occurs in almost any anatomical location [2]. Occasional cases have arisen in the field of therapeutic irradiation for other lesions [6–8].

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Genetic features

Over 90% of synovial sarcomas have a reciprocal balanced translocation t(X;18)(p11.2:q11.2) in which eight amino acids at the carboxy terminal of the *SYT (SS18)* gene on chromosome 18 are replaced with 78 amino acids of the carboxy terminal of the *SSX* gene on the X chromosome. The *SSX* gene has five variants of which *SSX1* (in about two thirds of cases) or *SSX2* are the usual components of the fusion gene [9], with a very small number involving *SSX4* [10]. Molecular variants within the fusion genes [11–13] and a t(X;20) translocation involving *SS18L* [14] have been described in single cases. The fusion gene seems to locate to a different nuclear domain from either of its components [15–17].

The functions of the gene products are unknown. The normal SYT protein is widely expressed, whereas *SSX* genes encode histone-binding proteins that are normally mainly expressed in the testis. In synovial sarcoma, cyclin D1 activity is increased, with induction of p21 (cyclin-dependent kinase inhibitor) but the oncogenic effect of the fusion is not clear, and other events might be required for sarcomagenesis. Alterations in other genes include expression of *ERBB2* in epithelial areas, upregulation of *IGF2*, repression of *CD44*, *PTEN* inactivation and mutations in genes associated with the Wnt pathway, notably *APC* and the genes encoding E-cadherin and beta-catenin [18]. Gene expression profiling has shown variably high expression of *ERBB2*, *IGFBP2* and *IGF2* in synovial sarcomas [19, 20], several differences in gene expression for *SYT-SSX1* and *SYT-SSX2* fusion types [21] and a possible genetic signature related to development of metastases [21].

Pathologic features

Microscopically, biphasic, monophasic spindle cell, poorly differentiated, calcifying/ossifying and myxoid subtypes have been described. The monophasic variant (Fig. 1) is the most common and has spindle cells, which are identical to those in biphasic tumours but can vary in shape from rounded to longer and more spindled. Poorly differentiated synovial sarcoma (Fig. 2) is characterised by frequent mitoses and necrosis, with rounding of cells, and can be focal or involve the whole tumour, which then resembles other small round cell sarcomas [22, 23] or less commonly carcinoma. All histological types of synovial sarcoma are focally immunoreactive for epithelial markers (cytokeratins in cytoplasm and epithelial membrane antigen on cell membrane) in over 90% of cases. There is diffuse immunoreactivity for bcl2 [24] and at least focal positivity for CD99 (which is more often cytoplasmic than membranous [25]), S100 protein, CD56 and calponin in many cases [26–28]. Calretinin [29] and beta-catenin [30] are also sometimes detectable in tumour cell nuclei. New antibodies selected based on data from gene profiling studies, such as TLE1 [31], or antibodies to fusion gene components such as SYT [32], though not wholly specific, might prove useful in diagnosis.

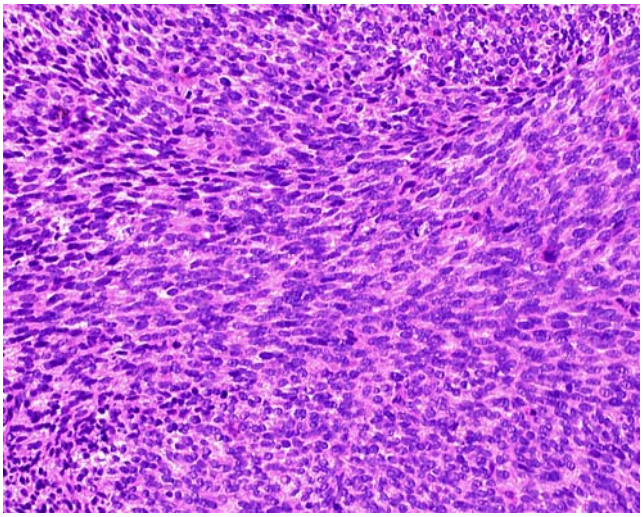

Fig. 1 Monophasic synovial sarcoma, showing fascicles of short uniform spindle cells with scanty cytoplasm

All histologic subtypes, regardless of immunophenotype, and those related to previous irradiation have the same range of genetic findings [7, 23, 33]. However, there is a relationship between degree of epithelial differentiation and type of fusion gene. Almost all biphasic tumours have the *SYT-SSX1* fusion [34, 35], whereas monophasic synovial sarcoma can display either fusion. The genetic changes are specific to synovial sarcoma [36, 37]. Thus, demonstration

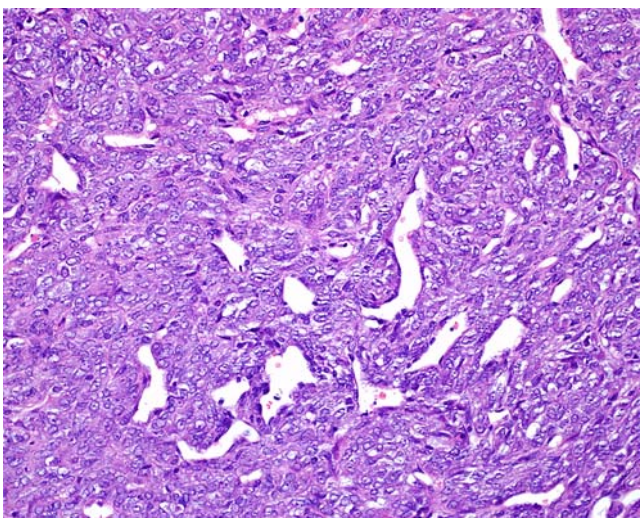

Fig. 2 Poorly differentiated synovial sarcoma composed of closely packed rounded cells with mitotic activity. There is a hemangiopericytic pattern

of the translocation or fusion gene transcripts is diagnostic and can distinguish synovial sarcoma from morphologically similar sarcomas, including malignant peripheral nerve sheath tumour and Ewing sarcoma/PNET.

Clinical features

Typically, synovial sarcoma is a tumour of young adults (mean age of 34), with nearly half the cases presenting in patients younger than 30 years [38]. There is a slight male predominance, and while cases with SYT-SSX1 fusion genes show an equal sex distribution, two thirds of those with *SYT-SSX2* gene rearrangement are found in females [38]. Primary tumours with *SYT-SSX1* fusion gene type tend to be more often located in the extremities [39].

Synovial sarcoma metastasizes in up to 50% of cases, to lung, bone and sometimes lymph node [38]. The 5- and 10-year survival figures are 36–76% and 20–63%, respectively [40–43]. Advanced stage, proximal location, male sex, age >40 years, tumour size >5 cm, poorly differentiated histology and Ki67 index [44] have been identified as adverse prognostic factors [42, 45]. Conversely, the outcome is more favourable in childhood, in very small sarcomas and in those with ossification. There may be a relationship between fusion type and prognosis although this is not straightforward [39]. Tumours with SYT-SSX1 have a higher proliferation rate and a lower 5-year metastasis-free survival compared with those with SYT-SSX2 [46], and it has been suggested that synovial sarcomas localised at time of diagnosis, which have the *SSX2* gene rearrangement, have a better outcome [38, 47]. However, this has not been confirmed in subsequent studies as a factor independent of grade [48] or tumour size [49]. The use of gene expression profiling for predicting metastasis has yet to be assessed [21].

About 55% of synovial sarcomas overexpress EGFR as detected by immunohistochemistry [50] and 73% express ERBB2 as shown by quantitative RT-PCR [50] and cDNA microarray analysis [20], raising the possibility of therapeutic interventions directed at receptor tyrosine kinases [51, 52] but results have so far been disappointing.

Alveolar rhabdomyosarcoma

Alveolar rhabdomyosarcoma is the second most common subtype of rhabdomyosarcoma after embryonal rhabdomyosarcoma [53]. It occurs principally in patients aged 10–25 years, with a median age of 16, with sporadic examples occurring in younger patients and older adults. The most common sites are the deep muscles of the extremities, but the tumour can also arise in the head and neck (nasal cavity, nasopharynx and paranasal sinuses, orbit, ear canal and oral cavity, including tongue), trunk, retroperitoneum and pelvis [54].

Genetic features

Approximately 75–90% of tumours categorised histologically as alveolar rhabdomyosarcomas have translocations which fuse the 5′ end (amino-terminal DNA-binding domain) of members of the *PAX* gene family, involved in formation of skeletal muscle satellite cells, with the 3′ end (C-terminal transactivation domain) of *FKHR (FOXO1)*, a gene which regulates myoblast differentiation [55–59]. About 70% harbour a t(2;13)(q35;q14), creating a *PAX3-FKHR* fusion, 15% have the t(1;13)(p36;q14) with formation of the *PAX7-FKHR* fusion, and occasional variants are reported in single cases [58, 60]. The fusion proteins are powerful transcription factors, and *PAX3-FKHR* expression has been shown to enhance cellular proliferation and invasion in rhabdomyosarcoma cell lines [61]. Additional changes, including those in *INK4a/ARF* and *TP53* pathways, may be needed for oncogenesis [62].

Pathological features

The typical microscopic pattern is one of nests of medium-sized rounded cells set within dense collagenous stroma (Fig. 3). The nests show central discohesion forming pseudoalveolar spaces, with a peripheral adherent layer of cells lining the ‘space’. The cells have ovoid hyperchromatic nuclei and scanty eosinophilic cytoplasm, and multinucleated cells with peripheral (‘wreath-like’) rings of nuclei are common. Rarely, there is increased clear

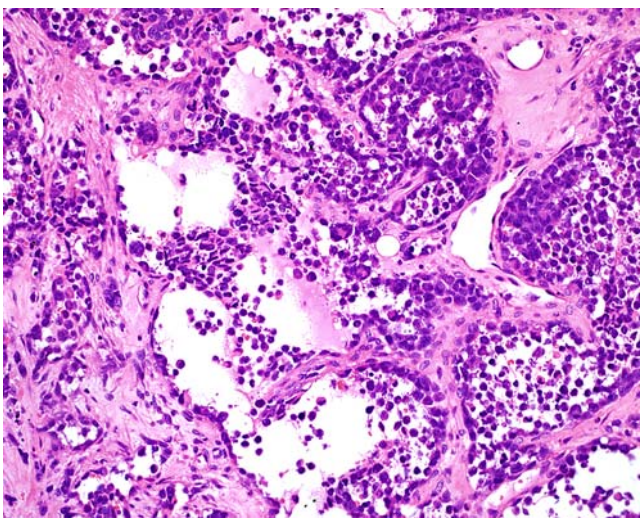

Fig. 3 Alveolar rhabdomyosarcoma showing nests of discohesive rounded cells, with rounded rhabdomyoblasts and multinucleated forms, in cellular fibrous stroma

cytoplasm due to glycogen accumulation, indicating designation as clear cell rhabdomyosarcoma [63–65]. Solid alveolar rhabdomyosarcoma [66, 67] is composed of sheets or large nests of rounded cells with hyperchromatic or vesicular nuclei, scanty cytoplasm and rare rhabdomyoblasts (Fig. 4). Solid variants of alveolar rhabdomyosarcoma are more often fusion negative than those with typical morphology [68]. There is otherwise no correlation between microscopic appearance and molecular abnormalities.

Immunohistochemistry for desmin is positive in almost all alveolar rhabdomyosarcomas in a high proportion of cells, and rhabdomyoblastic differentiation is confirmed by nuclear positivity for products of myogenic regulatory genes, including myogenin (myf4) and MyoD1(myf3). pRB immunoreactivity, related to allelic imbalance in the *RB1* gene, is more frequently detected in embryonal rhabdomyosarcoma than in alveolar rhabdomyosarcoma and may be an additional aid in differential diagnosis [69]. In some cases, genetic analysis is required to make this distinction.

Clinical features

Alveolar rhabdomyosarcoma is aggressive and metastasizes to lymph node, bone marrow, lung and other organs. Not uncommonly, especially with a head and neck or deep-seated primary tumour, the patient presents with an enlarged lymph node or with effects of marrow involvement such as leucoerythroblastic anaemia. Tumours with *PAX7-FKHR* fusion are less aggressive than those with *PAX3-FKHR*. They arise more often in the extremities, tend to remain localised and are associated with longer event-free survival [70] and longer overall survival in both locoregional [71] and metastatic disease [59]. Gene expression profiling can distinguish alveolar and embryonal rhabdomyosarcoma [72], has shown different profiles for fusion-positive and fusion-negative tumours [73] and has also identified molecular risk groups with varying outcome related to different gene signatures [74].

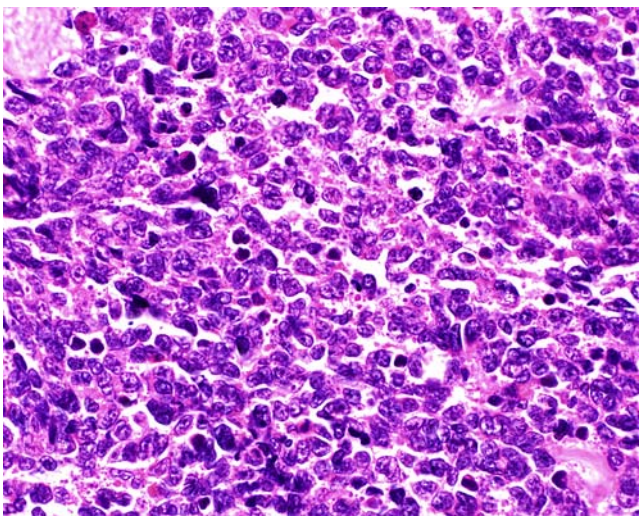

Fig. 4 Alveolar rhabdomyosarcoma, solid variant, composed of small round cells without obvious rhabdomyoblastic differentiation

Alveolar soft part sarcoma

Alveolar soft part sarcoma is a translocation sarcoma that does not correspond to any specific lineage. It is a rare tumour, accounting for <1% of all soft tissue sarcomas [75]. Its peak incidence is between 15 and 35 years of age, with a female predominance. The most frequent sites are the deep muscles of the thigh [76], especially the quadriceps, with sporadic cases in a variety of somatic and visceral locations, including bladder [77], cervix, vagina, uterus [78], mediastinum, heart [79] and GI tract. Head and neck locations, including tongue [80] and orbit [81], are common in childhood cases.

Genetic features

This tumour is characterised by an unbalanced (non-reciprocal) translocation, der(17)t(X;17)(p11;q25) [82, 83]. This results in fusion of the *TFE3* transcription factor gene (which contains a basic helix-loop-helix DNA-binding domain and a leucine zipper dimerization domain) on chromosome X with *ASPL* (*ASPSCR1*) on chromosome 17, which encodes a widely expressed protein of unknown function, to form aberrant transcription factors of two types that differ by one exon [84]. The fusion protein remains within the nucleus and can be demonstrated by immunohistochemistry using a specific antibody to the carboxy terminus of *TFE3* [85]. The same fusion is present in Xp11 (balanced) translocation-associated renal cell carcinomas, a category of papillary renal tumours occurring primarily in children and young adults [86, 87]. TFE3 nuclear immunoreactivity can also be demonstrated in some PEComas [88] and granular cell tumours [85] but whether that indicates a genetic abnormality of *TFE3* in those tumours is presently unclear.

Pathological features

Microscopically, there are nests of cells separated by fibrous septa and further delineated by thin-walled blood vessels (Fig. 5). The tumour cells are polygonal with distinct cell boundaries and contain rounded uniform vesicular nuclei and abundant finely granular or focally vacuolated cytoplasm. In childhood cases, there is often a

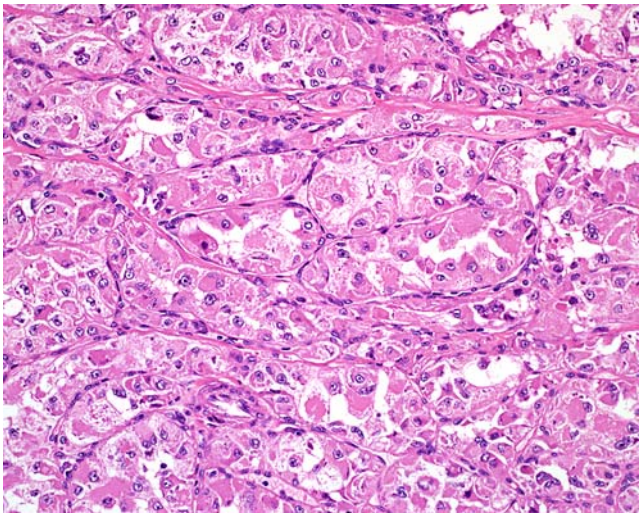

Fig. 5 Alveolar soft part sarcoma with nested pattern of polygonal cells with abundant cytoplasm

more solid pattern with the cells forming solid sheets or small closely packed nests and with reduced vascularity. No genetic differences between adult and childhood histological patterns have been identified.

The cytoplasm contains membrane bound rhomboidal crystals, which ultrastructurally display lattice-like filaments 4–6 nm in diameter with a periodicity of 10 nm [89, 90] and pre-crystalline granules. The latter contain monocarboxylate transporter 1, a proton-linked transporter for monocarboxylates (e.g. lactate and pyruvate) found in abundance in skeletal and cardiac muscle and its interacting partner CD147 (neurothelin) [91].

Immunohistochemistry using a specific antibody to the carboxy terminus of *TFE3* [85] is positive in nuclei of alveolar soft part sarcoma and also in translocation-associated renal cell carcinomas [86], some PEComas [88] and granular cell tumours [85].

Clinical features

Alveolar soft part sarcoma is relatively aggressive and metastasizes to lung, brain and bone but patients with localised disease can have a very prolonged course with survival of 77% at 2 years, 60% at 5 years, 38% at 10 years and 15% at 20 years (median 6 years) [76]. Patients presenting with metastatic disease have a median survival of 40 months and a 5-year survival of 20% [92]. Young adult [76] patients and those with small tumours have a better outcome, and childhood cases have a markedly better prognosis, especially for head and neck disease, with up to 100% 5-year survival [93]. There are no known genetic features, which predict behaviour or response to therapy, although a recent data showing activation of MET by the ASPL-TFE3 fusion protein have provided a rationale for examining MET kinase inhibitors in this setting [94].

Dermatofibrosarcoma protuberans

This is a relatively common neoplasm [95], which is more frequent in males, with a peak age incidence of 25–45 years, and also occurs in childhood and congenitally [96]. Dermatofibrosarcoma occurs mostly on the trunk and upper limbs as well as, to a lesser extent, other locations. The tumour begins as a dermal plaque or nodule and grows slowly, sometimes becoming multinodular. There are several morphologic variants, including pigmented dermatofibrosarcoma, giant cell fibroblastoma [97–100] and fibrosarcoma arising in dermatofibrosarcoma [101–106].

Genetic features

Dermatofibrosarcoma has a reciprocal translocation, t(17;22)(q22;q13.1) resulting in fusion of the genes *COL1A* (encoding the alpha 1 chain of collagen type 1, a heterotrimer) on 17q21-22 and *PDGFB1* (encoding the beta chain of platelet-derived growth factor, a homodimer) at 22q13 [107–111]. The same fusion is also seen in supernumerary ring chromosomes derived from t(17;22) [112], which are found in adult cases of dermatofibrosarcoma. Identical genetic changes have also been shown in morphologic variants, including the pigmented (Bednar tumour) [113] and granular cell [114] types, in the juvenile version giant cell fibroblastoma [114] (which more commonly has the linear translocation derivative than the ring chromosome [110]) and in examples of fibrosarcoma arising in dermatofibrosarcoma [115–117]. COL1A1-PDGFB fusion transcripts have also been identified in superficial CD34-positive fibrosarcomas without an antecedent or coexistent component of dermatofibrosarcoma [116]. The fusion gene transcripts can be detected by RT-PCR in paraffin-embedded material [96, 118]; this is not usually required for diagnosis but might be useful in guiding therapy, especially for superficial fibrosarcomas. Other rearrangements, including t(2;17) and t(9;22), are found rarely [119]. Gene expression profiling has shown high expression of a group of genes, which include *PDGFB*, osteonectin and apolipoprotein D [120, 121].

Pathological features

The typical lesion is composed of uniform elongated thin spindle cells with minimal cytoplasm and indistinct margins, in a striking and monotonous storiform pattern (Fig. 6). The tumour forms a nodule or ill-defined dermal

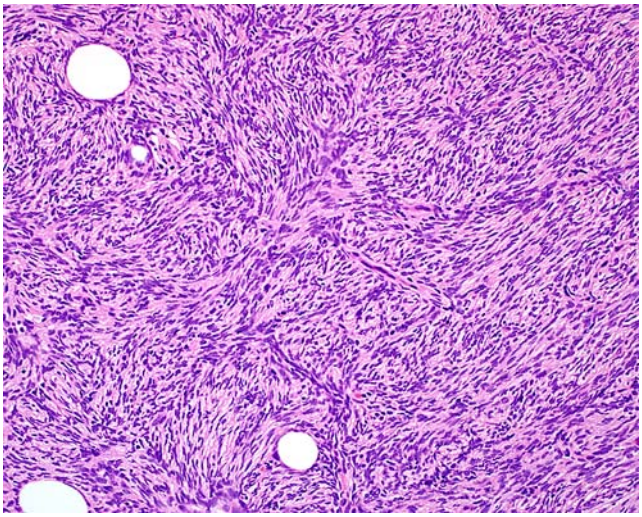

Fig. 6 Dermatofibrosarcoma demonstrating regular storiform pattern. The tumour infiltrates subcutaneous fat

plaque, which extends into subcutaneous fat with a characteristic honeycomb pattern, including layers of infiltrating tumour parallel to the skin surface. The lesional cells are diffusely positive for CD34. Apolipoprotein D, a glycoprotein component of high density lipoprotein, has been advocated as a diagnostic immunohistochemical marker [122], but is not specific for this tumour type [123].

Clinical features

Dermatofibrosarcoma recurs, especially if incompletely excised, but metastasis occurs in fewer than 5% of cases and usually follows multiple recurrences. Exceptionally, there is fibrosarcomatous (Fig. 7) or (very rarely) pleomorphic sarcomatous transformation, which can be regarded as a form of dedifferentiation.

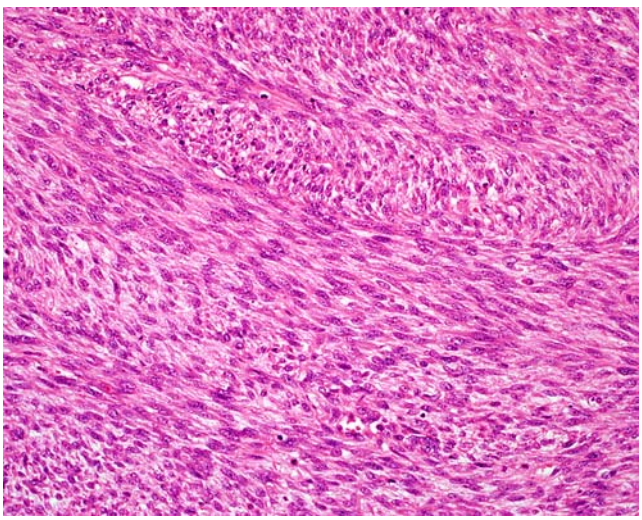

Fig. 7 Fibrosarcoma in dermatofibrosarcoma has a fascicular or herring bone pattern and frequent mitoses

PDGFR is a receptor tyrosine kinase, which in dermatofibrosarcoma is constitutively activated by autocrine or paracrine mechanisms as a result of overproduction of its ligand PDGFB [124], leading to cellular proliferation [125]. This has suggested the use of the tyrosine kinase inhibitors imatinib [126] and more recently sunitinib or sorafenib in locally advanced or metastatic disease [127–131], but fibrosarcomatous variants without the translocation do not respond [132, 133] so that genetic analysis is indicated before targeted therapy.

Low-grade fibromyxoid sarcoma

This fibrosarcoma variant has been recognised for over 20 years [134] but has recently been defined by specific genetic features, which have allowed appreciation of its wider range of microscopic appearances. This includes the tumour originally designated as hyalinizing spindle cell tumour with giant rosettes [135]. Low-grade fibromyxoid sarcoma presents as a well-defined mass in deeper soft tissues of extremities (especially the thigh), trunk and rarely other locations, including viscera, in young adults of either sex [136–142]. Examples located superficially have a higher incidence in childhood [143].

Genetic features

A t(7;16) translocation was initially reported in a hyalinizing spindle cell tumour [144] and a ring chromosome derived from the same chromosomes in metastatic low-grade fibromyxoid sarcoma [145]. Subsequently, a consistent balanced translocation, t(7;16)(q34;p11) in which the 5′ part of *FUS* from chromosome 16p11 fuses with 3′ part of *CREB3L2* (also known as *BBF2H7*), on chromosome 7q34, has been described in both low-grade fibromyxoid sarcoma and hyalinizing spindle cell tumour [146–148]. The breakpoints are mostly at exon 6 (and rarely 7) of *FUS* and exon 5 of *CREB3L2* [147–149]. *CREB3L2* is a member of the CREB3 family of transcription factors, which contain DNA binding and leucine zipper dimerization domains, and the fusion gene has increased transcriptional activity [150]. A smaller number have t(11,16)(p11;p11) with a FUS-CREB3L1 fusion gene consisting of the first nine exons of FUS and exons 5–12 from *CREB3L1* [148]. These findings have demonstrated that this sarcoma is morphologically heterogeneous and can be highly cellular or pleomorphic. No relationship has yet been shown, however, between genetic findings and microscopic appearances.

Pathological features

Histologically, low-grade fibromyxoid sarcoma shows fibrous and focally myxoid areas with a vaguely whorled pattern (Fig. 8). An abrupt transition to the myxoid foci is characteristic. Recurrent tumours can show increased cellularity, pleomorphism and mitotic activity. Up to 30% of cases have large rosette-like fibrous nodules bordered by more rounded tumour cells (Fig. 9). This variant was originally termed hyalinizing spindle cell tumour with giant rosettes [135] but is now known to be genetically identical to low-grade fibromyxoid sarcoma [146]. A relationship between low-grade fibromyxoid sarcoma and sclerosing epithelioid fibrosarcoma has been suggested [151].

The spindle cells in low-grade fibromyxoid sarcoma are often immunoreactive for EMA, at least focally [143, 151] and mostly negative for SMA, S100 protein and CD34. These must be distinguished from perineurioma, which has a mostly superficial location, elongated spindle cells with extended bipolar processes, perivascular whorls and immunoreactivity for claudin-1, GLUT1 and often CD34, as well as a characteristic ultrastructure. The genetic features of low-grade fibromyxoid sarcoma can be detected in paraffin section using FISH, RT-PCR [149, 151] or DNA-based PCR [152], with a sensitivity of over 80%, which is of diagnostic value.

Clinical features

Low-grade fibromyxoid sarcoma is a histologically low-grade sarcoma with metastatic potential. Reported rates of recurrence and metastasis were high in the early reports [136], which were retrospective studies of cases previously diagnosed as other tumours, with long follow-up. More recent studies indicate recurrence rates of 9–21% [137, 151]. In genetically confirmed cases, the metastatic rate was 27%, but more than 80% of metastases appeared after 9 years, indicating the need for long-term follow-up [151]. Superficial examples have a lower recurrence rate of 12%, and none has been reported to metastasize [143]. The finding at presentation of foci of higher grade sarcoma appears not to be prognostically adverse. No relationship has been shown between genetic findings and outcome.

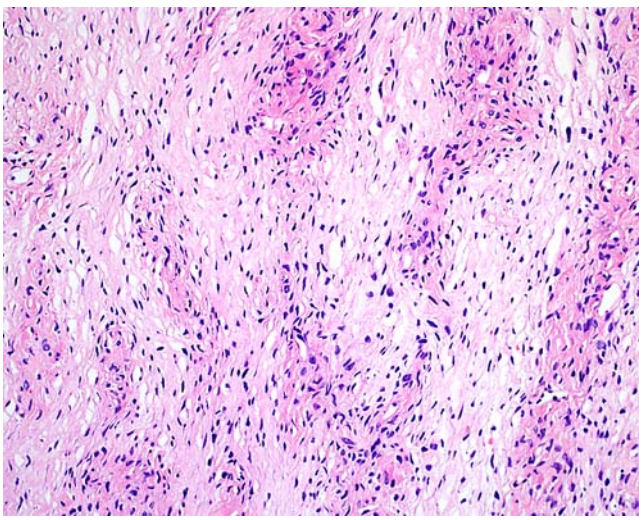

Fig. 8 Low-grade fibromyxoid sarcoma with alternating myxoid and fibrous areas. Note minimally pleomorphic spindle cells

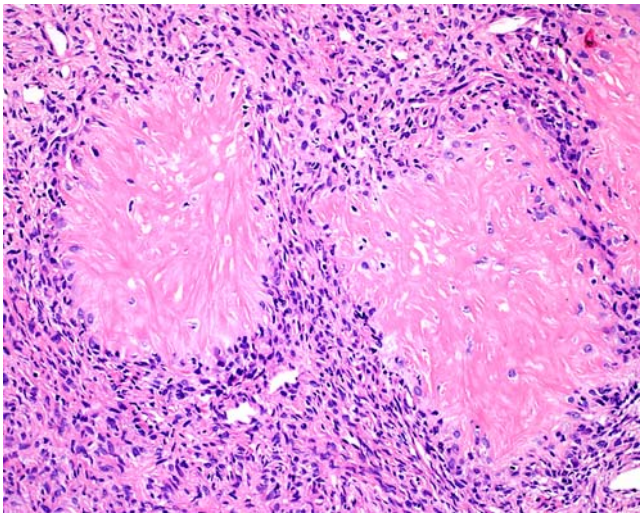

Fig. 9 'Giant' collagenous rosettes in low-grade fibromyxoid sarcoma. The cells adjacent to the collagenous zones tend to be more rounded

Infantile fibrosarcoma

This tumour occurs predominantly in the first 4 years of life, with a peak in the first 3 months, and presents as a rapidly growing mass, which can reach a large size. It arises in deep soft tissue, in limbs, where it can erode bone, and less commonly involves the trunk or head and neck region.

Genetic features

The majority of cases are diploid but reported cytogenetic abnormalities include trisomy 11, random gains of chromosomes 8, 11, 17 and 20 [153], deletion of the long arm of 17 [154] and a t(12;13) translocation [155]. Most cases of infantile fibrosarcoma have a specific translocation t (12;15)(p13;q25) [156–158] leading to fusion of *ETV6 (TEL)*, a member of the ets family of transcription factors,

on chromosome 12p13, and *NTRK3 (TRKC)*, which encodes a receptor tyrosine kinase for neurotropin-3 [159, 160] on chromosome 15q25. The helix–loop–helix dimerization domain of *ETV6* fuses to the protein tyrosine kinase domain of *NTRK3*. The fusion protein results in ligand-independent chimeric protein tyrosine kinase activity with autophosphorylation. This leads to constitutive activation of Ras-MAPK and P13K-AKT pathways via insulin receptor substrate-1, which is tyrosine-phosphorylated [161–163], and through the activation of *c-Src* [164]. The fusion protein also associates with TGF-betaII receptor, which can be oncogenic by leading to inhibition of TGF-beta receptor signals that mediate tumour suppression [165].

Identical genetic findings have been reported in the cellular variant of congenital mesoblastic nephroma, a microscopically similar tumour of the kidney [166, 167], and in secretory carcinoma of breast [168] and acute myeloid leukaemia [169], implying oncogenesis by lineage-independent activation of kinase-related signalling pathways.

Pathological features

Infantile fibrosarcoma is composed of uniform ovoid mitotically active spindle cells arranged in sheets or herringbone fascicles (Fig. 10). There is sometimes an apparently primitive round cell component but, as with other translocation sarcomas, cytologic atypia and pleomorphism are typically absent. A proportion of cases show positivity for SMA or desmin, with occasional expression of cytokeratin, CD34 and S100 protein. No relationship has been described between histologic appearances and genetic findings. However, the distinction from other sarcomas (especially synovial sarcoma and malignant peripheral nerve sheath tumour) can, when required, be made by genetic analysis, as well as careful attention to morphology and demonstration of the relevant immunophenotype.

Clinical features

Unlike adult fibrosarcoma, this is a tumour of intermediate malignancy: [170] About a third of cases recur but very few (0–5%) metastasize [171], and the 5-year survival exceeds 90% [172–174]. Most deaths from this disease are due to local complications. Complete excision is the treatment of choice [175]. Cases treated with pre-operative chemotherapy [171] or with chemotherapy alone [176] have done well. Axial tumours seem to behave more aggressively [177], but there are no histological or genetic predictors of behaviour.

Inflammatory myofibroblastic tumour

Inflammatory myofibroblastic tumour commonly arises in the abdomen, especially retroperitoneum or mesentery, where it can be solitary or multicentric, and rarely in other soft tissue sites [178, 179]. Similar tumours have been described in the lung under a variety of terms. The peak incidence is in the first decade of life, followed by adolescence, although examples occur in older adults. Patients present with symptoms relating to the mass lesion or with systemic features, including fever, anaemia and leukocytosis. A distinct subset arises in the urinary tract [180, 181], especially in the bladder; these are more frequent in males with a peak in the fifth decade, and

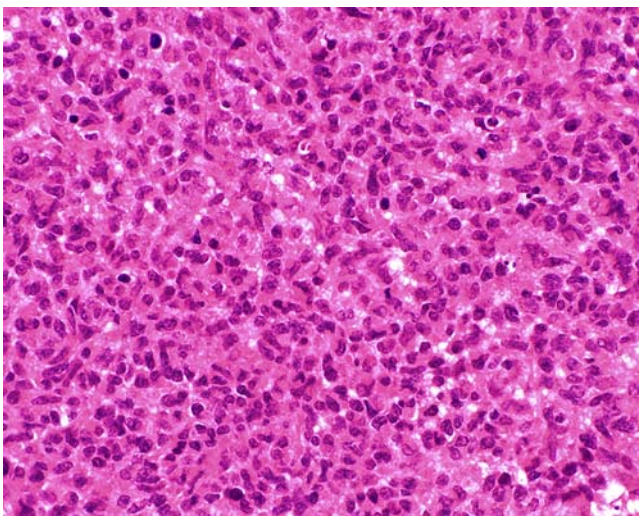

Fig. 10 Infantile fibrosarcoma is composed of uniform short spindle cells arranged in sheets or fascicles

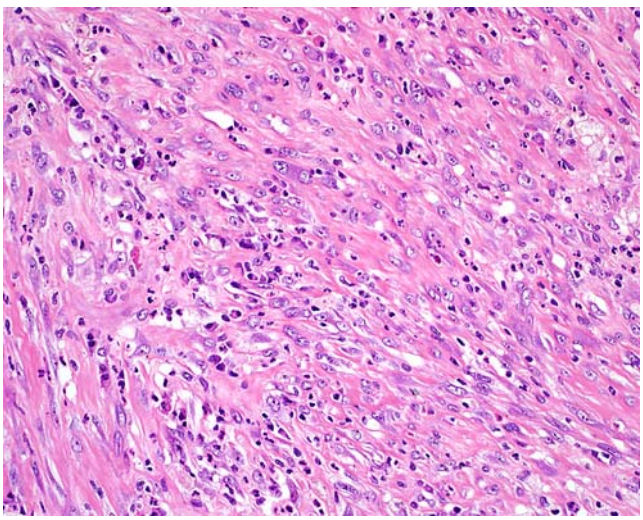

Fig. 11 Inflammatory myofibroblastic tumour displaying fasciitis-like and fascicular patterns with a marked admixture of plasma cells

about a quarter of the cases are associated with prior instrumentation [182, 183].

Genetic features

Inflammatory myofibroblastic tumour has fusions involving the C-terminal kinase domain of anaplastic lymphoma kinase (*ALK*) gene, located on 2p23, which encodes a receptor tyrosine kinase of the insulin growth factor receptor family that is normally expressed only in the central nervous system [184]. The resultant fusion protein is a constitutively active kinase. In inflammatory myofibroblastic tumours in pulmonary and other locations, the *ALK* gene can be rearranged with one of several other genes, including the actin-binding cytoskeletal proteins tropomyosin-3 (N-terminal coiled coil domain) as *TPM3-ALK* or tropomyosin 4 (*TPM4-ALK*) [185]. Other partners include *CLTC* (clathrin heavy chain gene, localised to 17q23) [186], *ATIC* at 2q35 (in a bladder tumour) [187], *RANBP2* at 2q13, *CARS* at 11p15 [188] and *SEC31L1* at 4q21 [189]. Identical rearrangements involving *TPM3*, *CLTC* and *ATIC* occur in anaplastic large cell lymphoma.

Pathological features

This is a variably cellular, usually bland fibroblastic–myofibroblastic proliferation with admixed plasma cells and lymphocytes. The appearances vary within the same tumour, with fasciitis-like, fascicular and sclerosing areas (Fig. 11). Related to the genetic changes, there is immunoreactivity for *ALK* in 36% to 60% [190–193] of cases, mostly in intra-abdominal, visceral or pulmonary tumours, and especially in those occurring in childhood [180, 193]. The staining is usually diffuse and cytoplasmic but varies with some fusion types: It can be granular (*CTLC*) or show nuclear membranous accentuation (*RANPB2*). It should be noted that immunoreactivity for *ALK* has also been reported in other tumours, including examples of malignant peripheral nerve sheath tumour, rhabdomyosarcoma and leiomyosarcoma [191, 194]. The *ALK* gene rearrangements can be detected in fixed tissue using FISH or PCR techniques [192, 195], which can be useful in diagnosis [183]; they are generally absent from the other sarcomas, which show sporadic ALK immunoreactivity [194].

Clinical features

About a third of cases recur after excision [196]. There is a relationship between *ALK* expression and morphology and behaviour of inflammatory myofibroblastic tumour: *ALK*-negative tumours occur more frequently in adults and display more nuclear pleomorphism and atypical mitoses, and in a recent series, all of six metastatic IMTs were *ALK* negative [193].

Conclusions

Non-EWS translocations are found in soft tissue sarcomas with a wide range of morphological manifestations and biological behaviour. Advances in knowledge of the genetics of these tumours are leading to more accurate diagnosis, by detection of translocations and gene fusions and by the use of new immunohistochemical reagents derived from specific fusion genes and their products or from gene profiling studies. The relationship between genetic changes and morphology is variable and mostly imprecise. The impact of genetic changes on behaviour is also variable within and between tumour types. There remain inconsistent findings in some prognostic studies, which are usually multifactorial.

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Conflict of interest statement I declare that I have no conflict of interest.

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