

Low Grade Sarcomas with CD34 Positive Fibroblasts, and Low Grade Myofibroblastic Sarcomas

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LOW GRADE SARCOMAS WITH CD34-POSITIVE FIBROBLASTS

Introduction Most fibroblastic lesions lack specific immunohistochemical markers and express only vimentin which is of no diagnostic value. A subset of benign and malignant fibroblastic tumors, however, is composed of CD34-positive cells. The human hematopoietic progenitor cell antigen (CD34) is a 110-kDa transmembrane cell surface glycoprotein encoded by a gene in the 1q32 region¹. It reacts with several non-hematopoietic tissues including vascular endothelium, endoneurial cells, and a subset of dermal dendritic interstitial fibroblastic cells in connective tissue, around blood vessels, nerves, smooth muscle bundles and hair follicles, and their tumors¹. CD34 is also variably expressed in a variety of mesenchymal neoplasms including some tumors of fibroblasts. These include dermatofibrosarcoma (DFS), fibrosarcoma arising in DFS, solitary fibrous tumor² and hemangiopericytoma, and a minority of cases of myxofibrosarcoma and myxoinflammatory fibroblastic sarcoma³ and pleomorphic hyalinizing angiectatic tumor⁴.

Dermatofibrosarcoma protuberans (DFS) is a relatively common lesion, which is more frequent in males with a peak age incidence of 25-45 years, and which occurs especially on the trunk and upper limbs. It begins as a dermal plaque or nodule and grows slowly, sometimes becoming multinodular. DFS recurs, especially if incompletely excised; metastasis occurs in fewer than 5% of cases and follows multiple recurrences; exceptionally, there is fibrosarcomatous or MFH-like transformation which is associated with a more aggressive course.

The lesion is composed of uniform elongated thin spindle cells with minimal cytoplasm and indistinct margins, in a striking and monotonous “tight” storiform pattern. The tumor forms a nodule or ill-defined plaque in the dermis which extends into subcutaneous fat with a characteristic honeycomb pattern including trabeculae or layers of infiltrating tumor parallel to the skin surface. Immunostaining shows strong diffuse CD34 expression, and focal reactivity for smooth muscle actin, but usually no significant staining for S100 protein. Some cases are CD117-positive, which has led to the suggested use of imatinib (Glivec) in locally advanced DFS or in metastatic disease^{5,6}.

The cell type of DFS is not clearly characterized ultrastructurally: histiocytic, perineural, pericytic and endothelial origin have all been suggested but most agree that there are variably developed features of fibroblasts (notably rough endoplasmic reticulum). The strong and diffuse CD34 expression supports the hypothesis that the tumor might be derived from (or differentiating towards) any of the local populations of normal CD34-positive fibroblasts - intradermal, periadnexal, or endoneurial. Occasionally, there are also focal peripheral filament bundles suggesting myofibroblastic differentiation. In keeping with this, some DFS are actin-positive, and focal areas of ‘myoid’ differentiation have been described in both DFS and, more frequently, in DFS-FS⁷⁻¹¹. In these, the cells have short, blunt-ended nuclei with eosinophilic cytoplasm which is SMA positive but desmin and CD34 negative, and electron microscopy has shown (mostly) myofibroblastic differentiation. It has been suggested^{12,13}, however, that this represents a change in the stroma rather than the lesional cells. The feature has no clinical significance. Factor XIIIa (which stains dermal “dendrocytes”) is generally not detectable in the principal lesional cells of DFS^{14,15}.

DFS has a reciprocal translocation, t(17;22)(q22;q13) (with a supernumerary ring chromosome) resulting in fusion of the genes *COL1A* (17q21-22) and *PDGFBI*(22q13)¹⁶⁻¹⁹. The same abnormalities have also been shown in fibrosarcoma arising in DFS, in which *COL1A1*-*PDGFB* transcripts have been demonstrated^{18,20}. Other rearrangements, including t(2;17) and t(9;22) have rarely been found in DFS²¹. Gene expression profiling has shown high expression of a group of genes which included *PDGFB* and *osteonectin*²².

Myxoid and pigmented variants of DFS are described. Rarer atrophic, palisading and granular cell variants are also recognized but lack clinical significance. *Myxoid DFS* can be diagnosed by the characteristic cytology as well as the (variable) CD34 positivity. It must be distinguished from a range of benign myxoid lesions and from myxofibrosarcoma (by absence of nuclear pleomorphism and the different

vascular pattern). *Pigmented DFS (Bednar tumor)*²³ has melanin-containing S100 protein-positive cells singly or in small clusters. This variant is incidentally more common in individuals with pigmented skin. It is cytogenetically identical to regular DFS²⁴, and can also undergo fibrosarcomatous change²⁵.

Fibrosarcoma can arise in DFS, both de novo and in recurrent lesions^{9, 26-31}. It is characterized by greater cellularity, fascicular architecture and increased mitotic activity. CD34 can be positive or negative in the fibrosarcomatous area³². The fibrosarcomatous component behaves relatively aggressively, with local recurrence in over 50% and metastasis in 15% of cases⁹. However, adequate local control of DFS with fibrosarcomatous changes, with clear surgical margins, can reduce both local recurrence and the incidence of metastasis³³.

Giant cell fibroblastoma is a rare childhood (and occasionally adult) lesion of dermis/subcutis, predominantly arising in back of thigh, groin and chest wall (in a similar distribution to DFS)^{28, 34-41}. GCF has recurrent potential. It is poorly circumscribed and infiltrative in skin and subcutis, with spindle and bland multinucleate cells in a fibrous and myxoid stroma, and focally forms cystic spaces lined by tumor (not endothelial) cells. Cellularity is variable, and both hypercellular and hypocellular (fibrous) areas occur. The lesional cells are CD34 positive and giant cell fibroblastoma has been recorded as recurring partially or completely as dermatofibrosarcoma protuberans, of either classical or pigmented types. This tumor is therefore currently considered to be a (juvenile) variant of DFS. The multinucleate cells are seen ultrastructurally to have a single nucleus with marked indentation and convolution. The cytogenetic abnormalities and molecular events in GCF are identical to those in DFS^{42, 43}.

Solitary fibrous tumor This neoplasm (SFT) was originally described in the pleura and has since been described in almost every site, including peritoneum, pericardium and mediastinum, liver, upper respiratory tract including nasal cavity, salivary gland and breast⁴⁴. SFT is increasingly recognized in soft tissues⁴⁵⁻⁴⁸. The lesion is circumscribed but rarely encapsulated, and is composed of plump or slender spindle or rounded cells in a collagenous background. The cells are bland and have scanty cytoplasm; multinucleated cells are sometimes present. Lesional cells are arranged in a "patternless" pattern, sometimes with alternating hyper- and hypocellular regions. In the latter, there is variable collagenization, which is focally dense although stroma is sometimes myxoid. The vessels are focally hemangiopericytomatous, and islands of mature fat can occur (lipomatous hemangiopericytoma⁴⁹⁻⁵²). Mitotic activity varies from 0-50 per 10 HPF, and some cases have necrosis or hemorrhage. Immunohistochemically, strong and diffuse CD34 and bcl-2 expression are a feature of this tumor type^{2, 53, 54}. Indeed, a CD34-negative tumor in an extra-pleural location should probably not be diagnosed as solitary fibrous tumor unless the other evidence is compelling⁴⁴. CD99 is also positive⁵⁵ and sporadically there is focal positivity for actin, S100 protein and (exceptionally) cytokeratin. Electron microscopy shows fibroblastic cells with very occasional myofibroblasts. In spite of the original reports of pleural tumors, SFT does not show evidence of mesothelial differentiation. A variety of genetic findings has been reported including loss of 13q, 4q and 21q; trisomy 21; and gains at chromosome 8 and at 15q; t(4;15)(q13;q26)⁵⁶, t(6;17)(p11.2;q23)⁵⁷, and t(9;22)(q31;p13)⁵⁸, and also, once again, rearrangements involving 12q13-15⁵⁷.

Predominantly myxoid SFT (myxoid change exceeding 50% of the tumor) is very uncommon, perhaps representing <5% of SFT⁵⁹. Cords of bland spindle cells lie in a vascular myxoid stroma, with focal cellular aggregates, and most also have areas of typical solitary fibrous tumor with variable collagenization and staghorn vessels. Nuclear atypia is absent. All cases are positive for CD34 and CD99. None of the reported cases experienced recurrence or metastasis.

SFT displays a spectrum of behavior. Recurrence is more likely with larger and histologically aggressive tumors, and atypical and malignant variants in soft tissue have been identified^{47, 60}. Suggested criteria for malignant SFT⁴⁴ are (1) presence in an otherwise typical SFT of at least two of: high cellularity with nuclear crowding and overlapping, pleomorphism, and mitoses >4/10 hpf (and one could perhaps add necrosis); and (2) development of sarcoma in the site of a previous SFT. CD34 expression can be lost in the malignant component.

Hemangiopericytoma Stout and Murray originally described hemangiopericytoma (HPC) in 1942⁶¹ with a further report of 25 cases in 1949⁶². Examination of these series suggests a heterogeneous group of neoplasms, including probable myofibroma. Stout himself stressed that the exact nature of the cells in these tumors had not been proved, and that there was no scientific basis in support of the designation. HPC is in fact becoming a diagnosis of exclusion as a wide variety of benign and malignant lesions show at least focally the non-specific but characteristic branching and staghorn open vascular pattern⁶³. Many cases that would previously have been termed hemangiopericytoma are now, on the basis of diffuse CD34 expression, diagnosed as solitary fibrous tumors (SFT).

Some Tumors with Hemangiopericytomatous Pattern

Cellular hemangioma	Congenital infantile fibrosarcoma
Myofibroma	Nerve sheath tumors
Intranodal myofibroblastoma	Leiomyosarcoma
Perivascular myoma	Liposarcoma (round cell)
Glomus tumor	Mesenchymal chondrosarcoma
Benign fibrous histiocytoma (deep)	Malignant fibrous histiocytoma
Solitary fibrous tumor	Synovial sarcoma
Giant cell angiofibroma	Malignant hemangiopericytoma
Hemangiopericytoma	

Pericytes are spindle cells surrounding small arterioles, capillaries and pre- and post-capillary venules, usually in a single complete or incomplete layer. Ultrastructurally, pericytes have overlapping processes and a continuous or interrupted external lamina lies between them and the endothelium. Variable features include micropinocytosis, microfilaments with dense bodies and junctions. Their immunophenotype varies with location: those around precapillary and postcapillary vessels express smooth muscle actin (SMA), whereas pericytes around capillaries are SMA negative⁶⁴. The latter perivascular cell has been considered to represent a persistent primitive mesenchymal cell that can, according to circumstance and specific location, differentiate into (vascular) smooth muscle cells, glomus cells, preadipocytes and osteoblasts⁶⁵. This cell type has also been postulated as the precursor cell of MFH⁶⁶. The group of tumors termed PEComas is supposedly derived from a SMA/HMB45 positive perivascular epithelioid cell but the normal counterpart of this cell has not been demonstrated⁶⁷.

The pericyte lacks specific morphologic features, and it is not clear that hemangiopericytoma, which is usually SMA negative, is composed of pericytes^{68, 69}. Nevertheless, cases still remain which are diagnosed as HPC after extensive investigation. A current definition might be: a tumor which has (a) spindled, plump, or rounded cells with small to moderate amounts of cytoplasm and indistinct cell margins; (b) a consistent HPC-vascular pattern throughout the entire tumor, with reticulin surrounding individual cells, and (c) the absence of specific differentiation, both morphologically and immunohistochemically. Such tumors usually occur in the deep soft tissue of extremities and retroperitoneum (here associated with hypoglycaemia and hypophosphatemia) but cases are reported in the breast, orbit, nasal cavity, and CNS as well.

CD34 positivity has been reported in apparent HPC, but the majority of cases formerly called HPC are now regarded as solitary fibrous tumors, especially when the CD34 expression is strong and diffuse. However, in SFT the HPC pattern is usually only focal. There is an occasional report of desmin or smooth muscle actin positivity, and FXIIIa and HLA-DR expression have been reported in a constant subpopulation of HPC cells, as well as a few cells with FVIIIIRAg⁷⁰. This is not, however, specific, as FXIIIa is present in many spindle cell tumors. Recently, scanty focal CD117 has been described in a small number of HPC⁷¹.

Neoplastic cells in HPC are described ultrastructurally as having overlapping processes with poorly developed junctions, focal myoid differentiation, and a fragmented external lamina between tumor cells and between them and the endothelium^{68, 69}. In SFT, the cells are fibroblast-like without external lamina, with rare myofibroblasts^{46, 60}. Occasionally myofilaments are seen in pericytes, and recently a group of tumors has been described with perivascular myoid differentiation⁷². This group included tumors with histologic features of infantile-type myofibromatosis, tumors with composite features of "hemangiopericytoma" and glomus tumor, and tumors with a distinctive concentric perivascular proliferation of spindle cells. Morphologic overlap among the groups suggests they are part of a single spectrum, termed perivascular myomas or myopericytomas, and some of these resemble and perhaps overlap with vascular leiomyoma. Strictly speaking, since they show specific differentiation these should be excluded from the HPC category.

Cytogenetic studies can exclude or identify specific tumor types with a hemangiopericytomatous pattern, such as synovial sarcoma with its t(X;18)(p11.2;q11.2)⁷³ and round cell liposarcoma which predominantly shows t(12;16)(q13;p11). Changes described in HPC have included t(1;3)(q22;q11) and t(7;12)(p22;q13)⁷⁴; t(12;19)(q13;q13.3)⁷⁵ and t(13;22)(q22;q11)⁷⁶. Thus, 12q13 is implicated⁷⁷ but this segment is rearranged in several soft tissue sarcomas and the findings are not specific⁷⁸.

The behavior of HPC cannot always be predicted from the histology. A benign HPC lacks cellular pleomorphism, necrosis and hemorrhage and has a low mitotic rate (either $< 4/10$ hpf⁷⁹ or $< 1/20$ hpf⁸⁰). With this definition, around 70% of HPC behave in a benign fashion, but some histologically benign cases have metastasized. The existence of a borderline grade (< 4 mitoses/10hpf, $< 5\%$ necrosis) has been suggested⁸¹ but the numbers are too small to assess the validity of this study. Clear-cut malignant cases, with necrosis and mitotic rates higher than above, have five- and ten-year survival rates of around 40% and 29% respectively.

In conclusion, most soft tissue tumors with a hemangiopericytomatous pattern can be given a more specific diagnosis. Many are now classified as solitary fibrous tumors, especially if they show varying cellularity and fibrosis and diffuse immunoreactivity for CD34 and bcl2 and often CD99. Some remain which can be termed hemangiopericytoma although there is no conclusive evidence that the tumor cells are derived from pericytes.

Lipomatous hemangiopericytoma. Soft tissue tumors in adults have been described with HPC pattern and a component of mature fat⁴⁹⁻⁵², mostly in males in deep soft tissue, mediastinum or retroperitoneum. They are circumscribed and display an intricate mix of HPC areas and adipose tissue. Perivascular or stromal hyalinization and focal myxoid change can be seen. Atypia is rare and the reported lesions have been benign. Cases are generally CD99 positive but expression of CD34 and bcl2 has been variable. Folpe et al found CD34 in 2 of 4 cases⁵¹, and in the series of Guillou et al, 7 of 12 were bcl2 positive and 10 of 13 were CD34 positive (one case expressed neither)⁵², so that at least some of these might represent variants of SFT⁵². *Sinonasal hemangiopericytoma* is a CD34-negative lesion with smooth muscle-like features that might represent differentiation towards a glomus or perivascular myoid cell⁸²⁻⁸⁴ and appears to be unrelated to HPC or SFT elsewhere.

Myxoinflammatory fibroblastic sarcoma This is a recently documented low-grade fibrosarcoma, which occurs mainly in digits, wrist and ankle regions, and predominantly in the subcutis. Montgomery et al⁸⁵ described 51 such cases as inflammatory myxohyaline tumor of distal extremities with virocyte or Reed-Sternberg-like cells. They occurred over a wide age range (4 – 81 years) and affected the sexes equally. 35 were in fingers, hand, wrist or arm, and 13 in toe, foot or lower leg. Many of the patients were treated aggressively but recurrences were noted in six of twenty-seven patients with follow-up. Almost simultaneously, a series of 44 apparently similar tumors in patients aged between 20 and 91 years was reported³ as “acral myxoinflammatory fibroblastic sarcoma”. These authors also noted a relation to tendon sheaths and joints in some cases. There was local recurrence in two thirds (67%) and several patients required amputation after repeated local recurrences, and histologically documented metastasis to lymph node in one individual. 5 tumors of the hand reported as “inflammatory myxoid tumor of the soft parts with bizarre giant cells”⁸⁶, appear to be the same entity. It is now known that this tumor can occur more proximally⁸⁷ and the term acral has been dropped in the 2002 WHO classification⁸⁸.

Myxoinflammatory fibroblastic sarcomas form infiltrative multinodular masses characterized by dense inflammation merging with myxoid to collagenous stroma. The myxoid zones contain (multi)vacuolated lipoblast-like fibroblasts, as seen in other myxoid fibroblastic lesions and representing stromal mucin within dilated RER. The inflammatory zones have scattered bizarre cells with vesicular nuclei and large inclusion-like nucleoli with abundant focally vacuolated cytoplasm, reminiscent of Reed-Sternberg cells or “virocytes”, some of which contain phagocytosed neutrophils. Ultrastructurally, these cells contain markedly dilated cisternae of rough endoplasmic reticulum, and perinuclear whorls of intermediate filaments. Other components include eosinophils, neutrophils, lymphocytes, plasma cells, Touton giant cells and siderophages, and fibrosis (including sclerosed and hyalinized areas). Normal and atypical mitoses are seen among the bizarre cells, and some cases display focal necrosis.

Immunostains are positive for vimentin and negative for CD30, CD15, and S100 protein; 4 of 13 cases were cytokeratin positive⁸⁵. In the Swedish series, 7 of 25 were CD34 positive, 2 were SMA positive in occasional bizarre cells, and Ki67 labeling index was less than one per cent³. Ultrastructural studies in this series demonstrated fibroblastic characteristics, and the ganglion-like cells are interpreted as modified fibroblasts. Clonal chromosome changes have been described in one case, which showed a complex karyotype with a reciprocal translocation t(1;10) (p22;q24) in addition to the loss of chromosomes 3 and 13⁸⁹.

LOW GRADE SARCOMAS OF MYOFIBROBLASTS

Introduction Myofibroblasts are modified fibroblasts^{90, 91} which were first described in granulation tissue⁹² and have since been identified in normal tissues and as the predominant cell in certain reactive lesions. In granulation tissue, in which they have been most intensively investigated, they are probably

derived from local fibroblasts^{92,2852}, in response to mechanical stress, and their functions, appearance and immunoprofile vary in relation to the phase of activity⁹³. This is reflected in the variable morphology of reactive lesions such as nodular fasciitis, and contributes to the range of appearances seen in other pathological conditions. Myofibroblast-like cells might sometimes be derived from vascular smooth muscle cells or from pericytes⁹¹, or by metaplasia as in spindle carcinomas⁹⁴. Some fibroblastic lesions have a component of myofibroblasts, but myofibroblasts do not apparently differentiate to smooth muscle cells. In wound healing, as epithelialization is completed, the myofibroblasts are presumed to disappear by apoptosis⁹⁵⁻⁹⁷.

Myofibroblasts are short, bi- or tripolar spindle-shaped or stellate cells, with crenated or ovoid pale-staining nuclei each of which has a single distinct, punctate nucleolus. There is sparse cytoplasm with indistinct cell margins. In addition to synthesizing collagens and other stromal components including fibronectin and laminin, myofibroblasts have contractile elements^{93, 96-99}. By electron microscopy, the cytoplasm has abundant rough endoplasmic reticulum and subplasmalemmal bundles of thin cytoplasmic filaments with dense foci. This differs from smooth muscle cells in which myofilament bundles with focal dense bodies are distributed throughout the cytoplasm, and which have surface features of pinocytotic vesicles, membrane thickenings and external lamina. The intracellular microfilament bundles traverse the cell membrane to join extracellular, fibronectin fibrils as the fibronexus adhesion complex. This is a specific cell to stromal attachment, which although distinctive (and not found in smooth muscle cells or fibroblasts) is seen in only occasional cells even in reactive myofibroblastic lesions¹⁰⁰. Other ultrastructural features of myofibroblasts include a prominent Golgi complex and collagen secretion granules in Golgi-derived vesicles. *Fibroblasts* have variable amounts of rough endoplasmic reticulum which can become distended with secretory products, but they lack external lamina, pinocytosis and organized cytoplasmic filaments. Fibroblasts express only vimentin, whereas myofibroblasts display various combinations of vimentin, actin isoforms (especially α -smooth muscle actin), desmin, and myosin^{101, 102}. Desmin is found less often in myofibroblastic neoplasms than in smooth muscle tumors¹⁰³, but both types of neoplasms can have detectable desmin, muscle specific actin (MSA) and smooth muscle actin (SMA). Myofibroblasts express calponin but usually lack h-caldesmon, a marker of smooth muscle differentiation¹⁰⁴. Some myofibroblastic lesions can show cytoplasmic (but not usually membranous) immunoreactivity for CD117 (c-kit); this varies with technical factors, including the antibody and whether there is antigen retrieval¹⁰⁵. In intra-abdominal lesions, this can lead to confusion with gastrointestinal stromal tumor⁷¹.

Benign neoplasms of myofibroblasts occur in soft tissues, bone and visceral locations. The term myofibrosarcoma, by analogy with the term fibrosarcoma, indicates a malignant tumor of myofibroblasts¹⁰⁶. Myofibrosarcomas display a range of appearances from fasciitis-like neoplasms to high grade sarcomas. Low- and intermediate-grade myofibrosarcomas are distinct from pleomorphic myofibrosarcomas, which are malignant fibrous histiocytoma-like tumors. Other low-grade malignant tumors with myofibroblasts include inflammatory myofibroblastic tumor and infantile fibrosarcoma, each of which has characteristic genetic abnormalities.

The myofibrosarcoma concept has been controversial. Many fibroblastic lesions have myofibroblasts, and the proportion of neoplastic myofibroblasts required is not defined. It is difficult to confirm myofibroblastic differentiation without electron microscopy, and there is no universal agreement on the ultrastructural criteria of the neoplastic myofibroblast^{107, 108}. Some authors require that stress fibers and the fibronexus, a characteristic feature of non-neoplastic myofibroblasts, be present for a diagnosis of myofibrosarcoma¹⁰². Since subcellular features can be incompletely or abnormally developed in malignant cells, the fibronexus has not been an absolute requirement for most investigators. This structure has, however, been reported in several myofibrosarcomas¹⁰⁹, and has been illustrated more often in case reports than it has been mentioned by their authors^{103, 110}. Identification of a cell type depends on several features, and the fibronexus is only one of the features used to define myofibroblastic differentiation.

It has also been held that sarcomas supposedly composed of myofibroblasts are actually poorly developed smooth muscle tumors¹¹¹. Low-grade leiomyosarcomas, however, usually have well-developed smooth muscle differentiation. Furthermore, although the cytoplasmic filament patterns can be somewhat similar in myofibroblasts and smooth muscle cells, the two cell types differ in other respects - unlike myofibroblasts, smooth muscle cells have external lamina, and cell membrane plaques as well as pinocytotic vesicles. Leiomyosarcoma and myofibrosarcoma can both display actins and desmin, but the latter is less often seen in myofibroblastic neoplasms. Also, in myofibrosarcomas, the actin staining is often manifested as a peripheral rim rather than throughout the cytoplasm¹¹². The paucity of h-caldesmon in myofibroblastic lesions additionally supports their separate identity^{104, 113}.

Thus, the ultrastructural features and immunohistochemistry, in conjunction with the morphology, are sufficiently distinctive to identify myofibroblastic differentiation in sarcomas. The two principal low grade lesions in this category are myofibrosarcoma and inflammatory myofibroblastic tumor.

Low-grade myofibrosarcoma is a distinctive neoplasm which occurs in soft tissues and bone as a fasciitis- or fibrosarcoma-like spindle cell sarcoma which infiltrates locally but rarely metastasizes. Myofibroblasts were observed in well-differentiated fibrosarcoma in 1975¹¹⁴, and the first 'sarcoma of myofibroblasts' was reported 3 years later¹¹⁵. About 50 cases have since appeared in the literature^{109, 116-127}.

Low- and intermediate-grade myofibrosarcomas occur at any age (range 7-85 years, mean 40) with a slight male predominance and tumor size ranging between 1.5 and 17 cm. Tumors can arise in extremities, trunk including breast, and retroperitoneum, but there is a predilection (up to one-third of cases) for the head and neck region in both soft tissue (including oral cavity especially tongue, face and neck), and bone, notably maxilla and mandible

Myofibrosarcomas can be found in subcutis or submucosa, but are mostly deep soft tissue or intraosseous tumors. They can be circumscribed, but mostly infiltrate irregularly along connective tissue septa or into skeletal muscle. The tumors are composed of mostly bland or focally pleomorphic stellate or spindle cells with tapered or ovoid nuclei with small nucleoli, and scanty or moderate amounts of eosinophilic cytoplasm. The patterns include fibrosarcoma-like fascicles, sheets or storiform whorls, with variable collagenous or myxoid stroma and scanty inflammation. Nuclear atypia is always present at least focally and usually mildly with scattered enlarged hyperchromatic nuclei, but larger atypical cells are sometimes seen. Mitotic activity is observed but necrosis is unusual. Recurrences tend to be more pleomorphic^{124, 128}, but in one example a breast metastasis from a grade 2 fibrosarcoma-like tumor resembled nodular fasciitis¹²⁴.

Electron microscopy shows myofibroblasts which have variable RER, cytoplasmic filament bundles, and in some cases minimal external lamina. Fibronexus structures and collagen secretion granules are rarely found. Low-grade myofibrosarcomas express actin (as a peripheral rim, beneath the cell membrane), and about one-half express desmin, usually in fewer cells^{123, 124}. These antigens can be expressed separately, with either a desmin positive/SMA negative or desmin negative/SMA positive immunophenotype¹²³. Calponin is diffusely positive, but h-caldesmon is only focally expressed in an occasional case¹²⁹. These findings are similar to those in nodular fasciitis, and differ somewhat from leiomyosarcoma, which usually displays diffuse h-caldesmon as well as calponin. Fibronectin¹³⁰ has been found in some myofibrosarcomas but not collagen IV or laminin. Rare myofibrosarcomas focally display cytokeratins or CD34¹²³, and one example had focal S100 protein positivity¹¹⁸. ALK-1 expression has not been reported.

Immunohistochemistry of smooth muscle and fibro/myofibroblastic tumors

	Des	SMA	MSA	S100	EMA	CK	CD34	Calp	hCald
Leiomyosarcoma	+	+	+	+	+	+	±	+	+
Myofibrosarcoma	±	+	±	-*	-	-*	-	+	-*
Fibrosarcoma*	-	-*	-	-	-	-	±	-	-

+ = diagnostically useful + = also sometimes found ± = inconsistently reported - = absent; * = very occasionally positive.

des = desmin; SMA = smooth muscle actin; MSA = muscle specific actin; EMA = epithelial membrane antigen; CK = cytokeratin; calp = calponin; hcald = heavy caldesmon

Low-grade myofibrosarcomas are indolent, but they can relapse and metastasize even after a long period. In one series, there was local recurrence in two of 11 patients and metastasis in one¹²³. In the series of Montgomery et al¹²⁴, 4 of 9 low-grade myofibrosarcomas, and three of four intermediate grade tumors recurred (one twice), and one intermediate-grade tumor which arose in the breast resulted in pulmonary metastasis after 12 months.

Myofibrosarcomas can resemble benign myofibroblastic lesions such as nodular fasciitis and fibromatosis, and other sarcomas, notably fibrosarcoma and leiomyosarcoma. Both clinical data and morphology are important for diagnosis since immunohistochemistry does not discriminate between myofibroblastic lesions and the immunophenotype overlaps with that of smooth muscle.

Nodular fasciitis is a mainly subcutaneous lesion which appears suddenly and grows rapidly but does not usually exceed 5 cm in diameter. There are myxoid, cellular and fibrous areas, often in different parts of the same lesion. Nuclear atypia and necrosis are absent. Myofibrosarcoma is more cellular and uniform than nodular fasciitis, and infiltrates more widely. Fibromatosis has files of slender spindle cells in dense collagen with slit-like blood vessels and mast cells, and lacks nuclear atypia. Fibromatosis also infiltrates skeletal muscle, but muscle fibres show atrophy rather than separation by tumor as in myofibrosarcoma.

Adult-type fibrosarcoma has a more herringbone-like fascicular architecture, and cells with scanty cytoplasm and elongated tapered nuclei. There is variable intercellular collagen and myoid markers are usually absent. Leiomyosarcoma typically has alternating fascicles of cells that are more parallel-sided with square-ended nuclei scattered paranuclear vacuoles. Caldesmon expression is more widespread. Other spindle cell sarcomas such as synovial sarcoma, malignant peripheral nerve sheath tumor, some examples of angiosarcoma and spindle cell rhabdomyosarcoma can be recognized by their morphology and by their specific immunophenotype. In head and neck and breast tumors, spindle cell carcinoma has to be excluded by use of multiple cytokeratin antibodies.

Inflammatory myofibroblastic tumor (IMT) is most commonly seen in the lung in childhood. Extrapulmonary tumors usually arise within the abdomen, (retroperitoneum or mesentery) as a solitary or multicentric mass^{131, 132} with peak incidence in the first or second decades with a slight female predominance. There are sometimes B-type systemic symptoms, anemia and hypergammaglobulinemia. Similar cases have also been termed inflammatory fibrosarcoma¹³³, but these conditions probably represent a single entity with a spectrum of morphology and behavior¹³⁴, i.e. a low-grade neoplasm of myofibroblasts.

IMT presents with multinodular and sometimes multiple firm white or yellow tumors up to 10 cm in diameter. Histologically (Fig 18) these are irregularly infiltrative lesions with three principal patterns, usually found in combination (1) fasciitis-like, with bland stellate or short spindle cells in a vascular, myxoid and inflamed stroma, including numerous plasma cells; (2) fascicular and fibrosarcoma- or leiomyosarcoma-like, again with marked inflammation; (3) hypocellular areas with hyalinization and calcification. The lesional cells are usually uniform, but atypical cells with prominent nucleoli¹³³, and ganglion-like or Reed-Sternberg-like cells can occasionally be seen¹³⁵.

Ultrastructurally, the cells are fibroblastic and myofibroblastic^{132, 133, 136}. Most cases are positive for SMA and MSA, and a smaller number for desmin; some (especially those in a submesothelial location) express cytokeratins. ALK immunostaining is positive in 36% to 60%¹³⁷⁻¹³⁹ of cases, with a granular pattern in cytoplasm or nucleus, and sometimes cell and nuclear membranous accentuation; the variant patterns possibly relating to different fusion genes. ALK expression, found predominantly in abdominal and pulmonary IMT in childhood, might be associated with an improved outcome.

Genetically, many IMT have clonal chromosomal abnormalities involving 2p22-24, and fusion of the anaplastic lymphoma kinase (ALK) gene, located on 2p23, which encodes a tyrosine kinase receptor, with tropomyosin 3 (TPM3-ALK) or tropomyosin 4 (TPM4-ALK) is found in a subset¹⁴⁰. A transcript involving ALK and CLTC (clathrin heavy chain gene, localized to 17q23) has additionally been reported¹⁴¹.

A third of cases, especially among intra-abdominal tumors, recur at least once. IMT can have increasing atypia with recurrence, and metastasizing sarcomatous change, with metastasis has been reported¹⁴². However, no factors have been identified which reliably predict behavior in these tumors. It has been suggested that the presence of atypia, ganglion-like cells, p53 expression and aneuploidy might be useful to identify IMT that might undergo pursue a more aggressive clinical course^{143, 144}. Surgical resection is the usual treatment for both primary and recurrent tumors.

The differential diagnosis relates to the various histological patterns. Retroperitoneal fibrosis has a distinctive clinical picture, is more inflammatory with mixed cells, and lacks pleomorphism. Fibromatosis has a distinctive architecture (intra-abdominal fibromatosis can have prominent keloidal collagen bundles) and is infiltrated by mast cells rather than plasma cells. Low grade myxofibrosarcoma has a more monomorphous pattern and lacks the prominent inflammatory component. Inflammatory MFH has atypical xanthomatous cells, while inflammatory leiomyosarcoma is more myoid, although the distinction can sometimes be difficult. Solitary fibrous tumor demonstrates CD34 expression, and sarcomatoid mesothelioma displays epithelial markers. Follicular dendritic cell sarcoma can masquerade as inflammatory pseudotumor in liver or spleen (see above); but is readily identified by expression of CD21,

CD23, and CD35. When there is intestinal wall involvement or a prominent fascicular architecture, the possibility of GI stromal tumor may be raised. This has shorter, plumper cells and less inflammation, and immunostaining with CD117 is positive with a membranous accentuation, in a different pattern from the weaker staining seen in myofibroblastic lesions.

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