Symposium 2

New entities in pathology of soft tissue tumors

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Adipocytic tumors: New entities and evolving concepts

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Introduction

Lipomatous tumors are the most common soft tissue lesions encountered by practicing surgical pathologists. Diagnostic criteria for both typical lipoma and liposarcoma are well established (1-3); however, in recent years numerous variants have been reported, both in the benign and in the malignant category. Moreover, the integration of genetics and pathology have supported proposals for significant changes in classification schemes that deserve comment (Table 1).

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<th>Table 1. Specific (primary) chromosome changes in adipocytic tumors.</th>
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Newly described adipocytic tumors

Myolipoma

Myolipoma (or lipoleiomyoma) was first reported in 1991 (4) as a deep-seated, usually large encapsulated benign lesion, arising in the abdomen, retroperitoneum or abdominal wall of adults. Histologically, myolipoma is composed of mature adipocytic tissue intermingled with bundles of differentiated smooth muscle. The application of myoid differentiation markers confirms the presence of dual adipocytic and smooth muscle differentiation.

Chondroid lipoma

Chondroid lipoma is a rare benign fatty tumor first described under a different name in 1986 (5) and fully categorized in 1993 (6). It usually presents as a well-defined, deep-seated lesion located in the limbs, trunk and head and neck region of adult females. Microscopically it is composed by an admixture of mature adipocytes, eosinophilic chondroblast-like cells and vacuolated cells set in myxochondroid background. One of the most striking features is the presence of vacuolated cells that cannot be distinguished from ordinary lipoblasts. Immunohistochemically, S-100 protein decorates most neoplastic cells. The absence of a plexiform vascular network is helpful in the differential diagnosis with myxoid liposarcoma. Extraskeletal myxoid chondrosarcoma can be distinguished due to its more pronounced lobular architecture associated with peripheral accentuation of cellularity, t also has to be stressed that despite popular belief, S-100 protein does not decorate more than 20% of extraskeletal myxoid chondrosarcomas (7).

Spindle cell liposarcoma

Spindle cell liposarcoma was first described in 1994 (8, 9) and represents an uncommon variant of well-differentiated liposarcoma. It tends to occur in adults, and to involve relatively often the subcutaneous soft tissue, at least in the first series. However, from the observation of a larger number of cases, the anatomic distribution of spindle cell liposarcoma seems to be comparable to that of the other well-differentiated liposarcoma subtypes. Spindle cell liposarcoma, whatever its location, tends to recur locally and may dedifferentiate. Morphologically, spindle cell liposarcoma is composed of a fairly bland neural-like spindle cell proliferation set in a fibrous and/or myxoid background and is associated with an atypical lipomatous component. Main differential diagnoses include spindle cell lipoma (composed of bland, sometimes palisading, CD34+ spindle cells, admixed with eosinophilic refractile collagen bundles); neofibroma (characterized by a less cellular S-i 00+ spindle cell proliferation with wavy nuclei); dermatofibrosarcoma protuberans (cytologically bland CD34+ spindle cell proliferation organized in a distinctive storiform growth pattern and characterized by its tendency to infiltrate the surrounding fat in a peculiar honeycomb pattern); malignant peripheral nerve sheath tumor (generally highly cellular tumors composed of taping or wavy spindle cells featuring perivascular accentuation of cellularity and focal S-100+ immunoreactivity in about 50% of cases); and, well-differentiated sclerosing liposarcoma (characterized by the presence of bizarre hyperchromatic stromal cells set in fibrillary collagen). The presence of an atypical lipomatous component permits distinction from low-grade fibromyxoid sarcoma (Evans’ tumor).

The description of spindle cell liposarcoma has generated some debate, which has been mostly focused upon an alleged similarity with the so-called “fibroblastic liposarcoma”, as defined by Dr. Hajdu. Fibroblastic liposarcoma, where illustrated, appears as a lesion unrelted to spindle cell liposarcoma, while considerable morphological overlap exists with myxofibrosarcoma. t is our opinion that spindle cell liposarcoma represents a distinctive clinicopathologic entity which is worthy of recognition. Interestingly, spindle cell liposarcoma exhibits chromosome changes (ring chromosomes and giant marker chromosomes) identical to those observed in the well-differentiated liposarcoma/atypical lipoma group.
Evolving concepts

Atypical lipoma/well-differentiated liposarcoma

Well-differentiated liposarcoma represents a group of tumors further subclassified by the World Health Organization (WHO) into adipocytic (lipoma-like), sclerosing and inflammatory subtypes. Great debate has been generated by the introduction (pioneered by Evans in 1979) of the term atypical lipoma or atypical lipomatous tumors (10, ii) to underline the fact that well-differentiated liposarcoma shows risk of local recurrence (about 30%) but no potential for metastasis. In our opinion, well-differentiated liposarcoma and atypical lipoma should be considered as synonyms that describe lesions identical both morphologically and karyotypically. Their use should depend on the degree of reciprocal comprehension between the surgeon and the pathologist in order to prevent either inadequate or excessive treatment (12).

Dedifferentiated liposarcoma

Dedifferentiated liposarcoma is considered by the WHO to be a distinct type of liposarcoma, in which transition from low-grade to high-grade nonlipogenic morphology within a well-differentiated liposarcoma is observed. First described by Evans in 1979 (13), such a phenomenon may occur either in the primary tumor (90%) or in recurrences (10%). The transition usually occurs in an abrupt fashion, however in rare cases can be more gradual and, exceptionally, low grade and high grade areas appears to be intermingled. Recently it has also been proposed that dedifferentiated liposarcoma should be further classified into low-grade and high-grade subtypes (14), but this remains rather controversial. Dedifferentiated liposarcoma may exhibit heterologous (most often myoid) differentiation in about 5% of cases, which apparently does not affect the clinical outcome. Recently, a peculiar “neural-like whorling pattern” of dedifferentiation has been described, the line of differentiation of which still needs to be fully elucidated (15). Surprisingly, the clinical outcome of dedifferentiated liposarcoma is less aggressive than in other high-grade pleomorphic sarcomas (16). Interestingly, in stark contrast with the complex karyotypic aberration observed in pleomorphic sarcomas, dedifferentiated liposarcoma usually exhibits the same basic cytogenetic anomalies as well-differentiated liposarcoma (17). At the molecular level, overexpression of MDM2 has been observed along with integrity of the p53 gene in the majority of cases. A significant increase in the level of both MDM2 overexpression and amplification in the high-grade areas has been observed which may account for the tumor progression in this subset of sarcomas (18).

Myxoid and round cell liposarcoma

Myxoid and round cell liposarcoma, even if still classified by the WHO as two distinct subtypes, share both clinical and morphological features. Lesions combining both patterns are very frequent and wide agreement exists in considering round cell liposarcoma as the high-grade counterpart of myxoid liposarcoma. Furthermore, myxoid and round cell liposarcoma share the same characteristic chromosome change, t(12;16) (19, 20), which, at the molecular level, fuses the CHOP gene on 12q13 with the FUS (or TLS) gene on 16p11 or with EWS on 22q12p. Lesions showing more than 10% of round cell (or hypercellular) areas should be classified as high grade (21), however, the prognostic meaning of a more limited round cell change remains to be elucidated.

Cutaneous liposarcoma

Although any liposarcoma subtype occasionally arises in the subcutis, the dermis seems to represent an exceedingly rare site of occurrence. Nonetheless, it has been recently shown that liposarcoma indeed can occur as a primary skin lesion (22). I often presents clinically as a dome-shaped or polyoid lesion which, histologically, most frequently shows high-grade morphological features. Primary cutaneous liposarcoma carries a comparatively good prognosis, although this needs to be confirmed by larger series.

Classification of liposarcoma

The latest edition of the WHO classification of soft tissue (2) recognized five distinct subtypes of liposarcoma (well-differentiated, myxoid, round cell, dedifferentiated and pleomorphic). However, during the last decade, the integration of morphology and genetics have greatly contributed to a more accurate classification of soft tissue neoplasms in general and of lipomatous tumor in particular. Considering currently available data, the most logical classification of liposarcoma is into the three following main groups: i) well-differentiated liposarcoma (including adipocytic, sclerosing, inflammatory, spindle cell and dedifferentiated variants), characterized by ring or long marker chromosomes derived from the long arm of chromosome 12; ii) myxoid and round cell (poorly differentiated myxoid) liposarcoma, characterized in most cases by a reciprocal translocation t(12;16)(q13;p11); and, iii) pleomorphic liposarcoma, characterized by complex karyotypes. Rarely, liposarcoma may combine features of different histological subtypes.

References

Tumors of uncertain histogenesis

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“Proximal-type” epithelioid sarcoma

Epithelioid sarcoma was recognized as a distinctive entity in 1970 when Enzinger (1) reported 62 cases of this unusual type of neoplasm. In its classical presentation, epithelioid sarcoma appears in the distal extremities (hand, wrist, forearm) of young adults as firm, slowly growing nodules of the subcutis, tendons and/or fascia. Ucleration of the skin may occur. A history of trauma is reported in up to 20% of the cases (2).

On microscopic examination, the conventional “distal” form of epithelioid sarcoma exhibits slight nuclear atypia, vesicular nuclei and small nucleoli. Transition between the two cell types is gradual and intercellular collagen deposition is usually marked. Frequently, the tumor nodules undergo central necrosis resulting in a pseudogranulomatous appearance simulating a benign necrobiotic process, such as a rheumatoid nodule or a granuloma annulare. Pseudoangiosarcomatous features due to cell disaggregation, dystrophic calcifications, bone formation, and accompanying chronic inflammation are also potential additional features (2).

Immunohistochemically, epithelioid sarcoma is characteristically immunoreactive for vimentin and epithelial markers (keratin and/or epithelial membrane antigen; EMA) (3-5). Half of the cases are also positive for CD34 (6) and occasional reactivity for smooth muscle actin has also been reported. Ultrastructurally, epithelioid sarcoma shows features of fibroblastic/myofibroblastic and epithelial (desmosome-like intercellular junctions, microvilli, tonofilaments) differentiation (7).

Epithelioid sarcoma is characterized by a protracted clinical course. Metastases which develop in about 40% of the patients, usually following repeated recurrences, involve primarily regional lymph nodes but also lungs, bone, and scalp (2, 8). Five- and 10-year overall survival rates range between 50% (2, 8) and 80% (9). The overall recurrence rate is about 80% at 10 years (10). Since conservative procedures are associated with an increased recurrence rate and reduced survival (9, 11), radical surgery (i.e., amputation) is advocated as the primary treatment of epithelioid sarcoma. Adverse prognostic factors in epithelioid sarcoma include male sex (2), advanced age at diagnosis, large tumor size (>5 cm) (8), deep location (9), presence of tumor necrosis (9), nuclear pleomorphism, high mitotic activity, presence of vascular and/or nerve invasion (12), multiple recurrences and presence or absence of regional lymph node metastases (12).

Recently, a special type of aggressive malignant soft tissue neoplasm thought to represent a “proximal” variant of epithelioid sarcoma has been described (13). In this variant, the tumors develop predominantly in the pelvis, perineum and genital tract (pubis, vulva, penis). Most of them are deep seated and they tend to occur in older adults more frequently than the “distal” conventional variant of epithelioid sarcoma.

Microscopically, “proximal-type” epithelioid sarcoma which often shows a multinodular pattern of growth is made of large epithelioid carcinoma-like cells with marked cytologic atypia, vesicular nuclei and prominent nucleoli. Rhabdoid features are also frequently observed and may even predominate in some lesions. Tumor necrosis, a common finding, seldom results in a granuloma-like pattern contrasting with that observed in the classical form of epithelioid sarcoma. Immunohistochemically, tumor cells show reactivity for keratin and EMA, singly or in combination, together with vimentin. About half of the cases are also positive for CD34, an antigen which is rarely expressed by carcinomas. Ultrastructural features of epithelial differentiation (tonofilaments and/or desmosomes) are also commonly observed.

Proximal-type epithelioid sarcoma involves a diagnosis of exclusion. Many entities have to be considered in the differential diagnosis including carcinoma, melanoma, epithelioid malignant peripheral nerve sheath tumor, smooth and striated muscle sarcomas, epithelioid angiosarcoma, rhabdoid tumor, as well as anaplastic lymphoma. Immunohistochemistry and/or electron microscopy are of paramount importance in this regard.

It is now admitted that, outside the kidney, the term rhabdoid tumor does not refer to an entity but rather to a distinctive phenotype shared by many tumors such as melanoma, carcinoma, mesothelioma and a large variety of sarcomas including both “distal” and “proximal” variants of epithelioid sarcoma (14-17). On occasion, the latter contains rhabdoid cells in such a quantity that distinction from an extrarenal rhabdoid tumor becomes almost impossible (18-20). Recent cytogenetic data showing chromosome 22q abnormalities in both tumor types would also support a close relationship between epithelioid sarcoma and rhabdoid tumor (21, 22). Renal rhabdoid tumors are known to be highly malignant tumors with poor prognosis. Accumulated data also indicate that rhabdoid features in extrarenal malignant tumors correlate with aggressive behavior, multimodal therapy resistance, and a rapidly fatal outcome. In keeping with the latter observation, “proximal-type” epithelioid sarcoma seems also to be associated with a more aggressive clinical course and earlier tumor-related deaths as compared with the more indolent behavior of conventional epithelioid sarcoma (2, 5, 13). However, it is not clear yet whether this dismal behavior is related to the prominent rhabdoid phenotype or merely to classical prognostic factors such as tumor size, depth, proximal/axial location, resectability, vascular invasion, etc.
The histogenesis of epithelioid sarcoma is still a matter of controversy. Although proximal-type epithelioid sarcoma shows striking resemblance to a carcinoma with regard to its morphology and immunohistochemical profile, it differs from the latter in its lack of connection with detectable epithelial structures and its 0034 immunoreactivity (in at least in 50% of the cases). The recent demonstration of V-cadherin rather than C-cadherin expression in epithelioid sarcoma militates also against the carcinoma hypothesis and gives support to the mesenchymal derivation of such a tumor (23).

**Pleomorphic hyalinizing angiectatic tumor of soft parts**

Recently characterized (24), the pleomorphic hyalinizing angiectatic tumor (PHAT) is a nonencapsulated mesenchymal lesion that occurs mostly in lower extremity subcutaneous tissues of middle-aged patients with no sex predilection. Clinically, it may resemble a hemangioendothelioma (chondroid syringoma) than in mixed tumors/myoepitheliomas of soft tissue. In the original series, tour tumors out of eight (50%) with available follow-up recurred but none of them metastasized.

Grossly, most PHAT show infiltrative margins; a minority of lesions being well circumscribed. Histologically, this lesion presents as a proliferation of spindle and/or pleomorphic cells in which one can find clusters of ectatic thin-walled vessels surrounded by prominent fibrin/collagen deposition. Most often, the lesion has infiltrative borders; intratumoral hemosiderin deposits may be prominent and organized intravascular thrombi are commonly observed. The spindle and pleomorphic cells possess hyperchromatic, pleomorphic nuclei with frequent prominent intranuclear pseudoinclusions. Mitosis are very rare (less than 1 per 50 high-power fields). Chronic inflammatory cells can be found in or surrounding the lesion as well as intratumoral mast cell collections. The spindle/pleomorphic cells in PHAT are negative for S100 protein and vascular markers (0031, factor VIII) but half of the tumors in the original series and in a subsequent report (25) were CD34 positive. Reactivity for factor XIIIa has also been observed (25).

Because of the cellular pleomorphism, the hemorrhagic changes, and the occasional presence of prominent cytoplasmic intranuclear inclusions, the lesion may be confused with a high grade storiform/pleomorphic variant of malignant fibrous histiocytoma or a vascular variant of this, although one should be struck by the contrast between the low mitotic rate and the marked cellularity and pleomorphism of the lesion. The peculiar clustered arrangement of vessels with heavy perivascular fibrin deposition is another clue to the diagnosis. PHAT of soft tissues is more likely to be confused with a benign lesion, especially an ancient schwannoma, and perhaps a melanotic schwannoma in cases with heavy intratumoral hemosiderin and/or calcification deposition or an ancient hemangioma (so-called symplastic hemangioma) (26). The lack of immunoreactivity for S100 protein and vascular markers allows distinction from those latter entities but it should be noted that 50% of the tumors are CD34 positive (24, 25), a reactivity usually not observed in malignant fibrous histiocytoma but common in neurilemoma.

**Mixed tumors and myoepitheliomas of soft tissue**

Mixed tumors in the salivary glands (pleomorphic adenoma) and the skin (chondroid syringoma) are well-known entities. Microscopically, these tumors are made of a varying admixture of epithelial and myoepithelial elements within a hyalinized to chondromyxoid stroma, the term myoepithelioma being restricted to those tumors composed exclusively of myoepithelial cells. Recently, attention has been drawn to the possible occurrence of mixed tumors and/or myoepitheliomas in the subcutis and deep soft tissues (27, 28). Based on the study of Kilpatrick et al. (27), who reported on 19 cases of such lesions, mixed tumors and myoepitheliomas of soft tissues would originate predominantly in limbs (hand, forearm, ankle, foot) and limb girdles (shoulder, thigh, inguinal region) of middle-aged adults with a male sex predominance. Trunk and head and neck regions are less frequently involved, The lesions are located within the subcutis in their great majority, encroaching occasionally upon dermis; a minority of them may be found in deep subcutis soft tissues. Mixed tumors and myoepitheliomas of soft tissue behave as benign lesions in most cases. A minority of patients, however, develop local recurrence or metastases. No specific pathological feature, including the mitotic rate, seems to correlate reliably with relapse. With regard to recurrences (two patients out of 10 in the series by Kilpatrick et al.; 27), it is likely that they have more to do with an insufficient surgical procedure rather than with intrinsic tumor biological properties. Hence, complete excision with a clear margin seems to be the treatment of choice for those lesions.

Macroscopically, most mixed tumors of soft tissue are predominantly well circumscribed and lobulated, measuring usually less than 5 cm in maximal diameter. Histologically, they are characterized by the presence of cords and strands and/or ductules of epithelioid cells and/or nests of spindle cells within a hyalinized to chondromyxoid stroma. In rare cases, some tumors may predominantly be composed of myoepithelial spindle cells. Epithelioid cells are often large and round with abundant, clear to eosinophilic cytoplasm. Occasionally, they may have a plasmacytoid appearance and/or may contain prominent cytoplasmic hyaline inclusions. Myoepithelial cells show either a round/ovoid or spindle cell cytology, epithelioid and myoepithelial cells coexist in varying proportions in the same tumor. Nuclear atypia is minimal and mitotic figures are rare even in those tumors which proved to metastasize. The cartilaginous component which fails to show any features of malignancy may be mature and/or myxoid. Predominantly myxoid lesions should be differentiated from an extraskeletal myxoid chondrosarcoma, which is the main differential diagnosis. Foci of squamous differentiation, osteoid and cartilage production as well as the presence of an adipocytic component are potential additional morphological features.

Most epithelial and myoepithelial cells in mixed tumors and myoepitheliomas of soft tissue express cytokeratin and S100 protein, respectively. In addition, some myoepithelial cells may also express smooth muscle actin, muscle-specific actin and, more rarely, desmin and glial fibrillary acid protein (GFAP). EMA reactivity is generally restricted to ductules structures.

In the subcutis, mixed tumors and myoepitheliomas of soft tissue should be differentiated from chondroid syringoma. The latter (also called pleomorphic adenoma or mixed tumor of the skin) presents generally as a small (often less than 2 cm), well-circumscribed benign lesion of the head and neck (as opposed to mixed tumors of soft tissue which predominate in limbs), located in the dermis or in the very superficial portion of the hypodermis. Microscopically, myoepithelial differentiation is usually less pronounced in chondroid syringoma than in mixed tumors/myoepitheliomas of soft tissue. In deep soft tissues, mixed tumors/myoepitheliomas should be differentiated from extraskeletal myxoid chondrosarcomas. Epithelioid cell reactivity for epithelial markers and myoepithelial cell positivity for smooth muscle actin and/OR GFAP are crucial in making the distinction. S100 protein is not a discriminating marker since it may
also be positive in myxoid chondrosarcoma (29). Tumors predominantly made of myoepithelial cells that display a marked plasma-cytoid and/or rhabdoid appearance are prone to be confused with a carcinoma, a melanoma or an epithelioid-appearing sarcoma. Parachordoma, another SI00 positive lesion of the extremities, also enters the differential. As opposed to mixed tumors of soft tissue, parachordoma is negative for epithelial markers.

References


Small round cell tumors of childhood

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Introduction

“Small round cell tumor” is the traditional generic name given to a group of undifferentiated tumors occurring with predilection in children and young adults in which light microscopy alone is not always sufficient to give an accurate diagnosis. The new immunohistochemical and molecular techniques have had a deep impact on the diagnosis and classification of tumors of this group, and several new entities have been delineated over the last few years. This review is mainly focused on rhabdomyosarcomas and desmoplastic small round cell tumor.

Rhabdomyosarcoma is the most common soft tissue sarcoma in childhood. The traditional classification scheme included the four following histological subtypes: embryonal, botryoid, alveolar and pleomorphic. The first two are associated with a good prognosis, and the latter two with a poor outcome. Pleomorphic rhabdomyosarcoma is virtually never seen in childhood. During the last few years two new subtypes of rhabdomyosarcoma have been recognized, one as a variant of the embryonal type with a particularly good prognosis, and the other as a subtype of alveolar rhabdomyosarcoma, which can be easily confused with the former and is accompanied by a challenging differential diagnosis.

Embryonal rhabdomyosarcoma, spindle cell variant

It was originally reported by Cavazzana et al. in 1992 (1) as a prognostically favorable variant of rhabdomyosarcoma, and is characterized histologically by elongated fusiform cells. It usually appears in male children (mean age, 6; M:F Ratio, 6), the most frequent location being the paratesticular area, followed by the head and neck region. Microscopically the tumor is arranged in well-circumscribed nodules of spindle cells, similar to fetal myotubes at a late stage of development. Two different histological patterns can be seen. The most usual form corresponds to long fascicles similar to those seen in fibrosarcoma or smooth muscle tumors. In the other type, the cells are arranged in whorls or short fascicles embedded in a highly collagenized stroma. Vimentin, actin, desmin and myoglobin are more frequently expressed than in classical embryonal rhabdomyosarcoma, which is consistent with a higher degree of skele-
tal muscle differentiation, also evident at the ultrastructural level. The better prognosis of the spindle cell variant compared with classical embryonal rhabdomyosarcoma (1), was confirmed in a further clinicopathological study carried out on paratesticular rhabdomyosarcoma (2). The 5-year survival rate was 88% for the spindle cell variant, and 66% for the classical variant. Interestingly, several cases have recently been reported in adults (3) and have shown similar pathological features but are associated with a less favorable outcome.

**Alveolar rhabdomyosarcoma. solid variant**
This entity was described early this decade when subsets of patients diagnosed with embryonal rhabdomyosarcoma were reported to have tumors with compact small round cell histology, with the unfavorable prognosis of alveolar rhabdomyosarcoma but lacking an evident alveolar pattern (4). They usually arise as alveolar rhabdomyosarcoma in the soft tissues of the trunk and extremities of adolescents or older boys. Light microscopy shows a solid pattern of growth, sometimes with a small amount of intervening stroma that delineates tumor cell nests. Actually a closer look reveals that their cytology, with a coarse chromatin pattern and nucleoli, is similar to that of alveolar rhabdomyosarcoma. Muscle differentiation is evident when antibodies for MyoD1, desmin or actin are used, although myoglobin reactivity is seldom found. Z-bands or other ultrastructural signs of rhabdomyoblastic differentiation can be found in about 60% of cases. Interestingly, solid alveolar rhabdomyosarcoma display the same molecular features of alveolar rhabdomyosarcoma [t(2;13)(t(1;13), and their related gene fusions, namely PAX3-FKHR, and PAX7-FKHR]. In contrast, it lacks the genetic loss at 11p15, a characteristic feature of embryonal rhabdomyosarcoma. The differential diagnosis includes lymphoma, neuroblastoma, and, most importantly, extraskeletal Ewing’s sarcoma/primitive neuroectodermal tumors (PNET). The presence of PAX3/7-FKHR fusion transcripts, readily detectable by RT-OR or FISH, along with an appropriate immunohistochemical panel are of help for the differential diagnosis.

**Desmoplastic small round cell tumor**
The first reported series of desmoplastic small round cell tumor (DSRCT) (5) describes a distinct undifferentiated neoplasm that usually affects male adolescents, and presents clinically with widespread abdominal serosal involvement. Histologically, small round tumor cells are arranged in nests or trabeculae and embedded in a desmoplastic stroma, and immunohistochemically display a characteristic polyphenotypia. Subsequent cytogenetic and molecular studies reported a consistent t(11;22)(p13;q12) resulting in a EWS-WT1 gene fusion, whose products can be detected at the RNA and protein levels (6). This tumor is being diagnosed with increased frequency, and although the presence of the translocation and fusion of EWS and WT1 genes are consistent features (7), there is a greater degree of clinical, pathological, and molecular variation than originally reported.

There is a striking predominance of male patients (5/1), with a mean age of 22 years (range 6-49). The overwhelming majority of tumors (95%) are intraabdominal, although four cases have been described in the pleural cavity, one in the posterior cranial fossa, and one in the hand (8). Typical histology, as described above, is seen in most cases, although considerable histological variation is reported in other cases (7). The size of the tumor nests varies, from small clusters to large solid areas, with or without central necrosis. A prominent vascular hyperplasia can be sometimes seen in the stroma, as well as some foci of epithelial differentiation in the form of glands, rosettes, or trabecular arrangements. Although cells are usually small, foci of pleomorphic cells can also be seen. The immunohistochemical profile of DSRCT consists of reactivity to keratins, desmin, neuron-specific enolase (NSE), vimentin, and epithelial membrane antigen (EMA) in various combinations. In contrast, muscle common actin or myogenin are not detected, which could be of help in the differential diagnosis with rhabdomyosarcomas. Reactivity for MIC2 (O13) is seen in 19% of cases (7), but it shows a cytoplasmic staining in contrast with the membranous pattern displayed by Ewing’s sarcoma cells.

The EWS-WT1 chimeric transcript has been found in 97% of studied cases. This consistency is useful for the molecular differential diagnosis among small round cell tumors, many of them also having specific chimerical transcripts (Ewing’s/PNET, alveolar rhabdomyosarcoma) (9). This consistent presence of the fusion gene also suggests that this genetic event is of importance in the development of DSRCT. In fact, the fusion protein functions as an aberrant transcription factor, modulating the expression of genes that overlap with those normally regulated by WT1. Interestingly, one of those genes is PDGFA, a potent fibroblast growth factor that contributes to the characteristic reactive fibrosis associated with this unique tumor. Furthermore, the serosal lining of the body cavities, the most usual site for DSRCT, is a structure that has an intense transient fetal expression of the WT1 gene. This gene could then be related to the normal development of specific mesodermal tissues close to the serosal lining. Inappropriate activation of WT1-responsive genes due to the EWS-WT1 fusion protein could explain why DSRCT commonly arises in the coelomic cavities.

Although DSRCT is associated with a poor prognosis, multimodal therapy, including debulking surgery, chemo- and radiotherapy, suggest that long-term survival is possible when aggressive therapy is instituted. Isolated case reports on other polyphenotypic tumors have been recently published. These tumors shared similar morphological features with DSRCT, but showed different chimerical transcripts (EWS-FL1I and EWS-ERG) characteristic of Ewing’s sarcoma/PNET (10, 11, Gerald W., personal communication). These findings suggest that classification of this group of primitive tumors is not yet fully established, and new entities could be described in the years to come.

**References**
Vascular tumors

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Introduction

Vascular tumors are a large and heterogeneous group of mesenchymal lesions and span a broad spectrum of morphology and clinical behavior. Despite recent developments, the exact classification of vascular tumors is still problematic because conceptual confusion persists in the distinction between vascular malformations, reactive and truly neoplastic endothelial lesions. In addition, there exists an expanding group of vascular neoplasms in which morphological features do not predict reliably the clinical behavior, as well as benign vascular neoplasms that closely mimic more aggressive lesions (i.e., angiosarcoma, Kaposi’s sarcoma) (1). In this review, recently characterized vascular tumors of skin and soft tissues are briefly discussed, including benign and low-grade malignant lesions which simulate early forms of Kaposi’s sarcoma and aggressive angiosarcoma.

Microvenular hemangioma

Microvenular hemangioma is a distinctive vascular proliferation in the spectrum of capillary hemangiomas which is easily mistaken for early Kaposi’s sarcoma or cutaneous angiosarcoma. Clinically, most cases present as a small, enlarging papule on the limbs of young to middle-aged adults (2). Histologically, a proliferation of irregularly branching, thin-walled venules is seen, which infiltrate the sclerotic dermal collagen. These narrow neoplastic vascular structures are lined by inconspicuous, sometimes plump endothelial cells surrounded by actin-positive pericytes. No prominent inflammatory infiltrate or hemosiderin deposits are noted. The evidence of lobular aggregates of small capillaries in deeper parts of some lesions suggests a close relationship to ordinary capillary hemangioma (3). The main differential diagnosis of microvenular hemangioma is patch-stage Kaposi’s sarcoma. However, the lack of hemorrhage and lack of associated lymphatic or venous channels suggests a neoplastic process. The diagnosis is supported by the presence of abnormal vascular structures in the skin and subcutaneous tissue, and the absence of an associated lymphocytic infiltrate. Further differential diagnoses include I-cell disease, Rendu-Osler-Weber syndrome, and Loeffer syndrome.

Further differential diagnoses include I-cell disease, Rendu-Osler-Weber syndrome, and Loeffer syndrome. These lesions are characterized by a disturbance of angiogenesis and are associated with multiple cutaneous and systemic manifestations, including aneurysms, arteriovenous malformations, and telangiectasias. The differential diagnosis of microvenular hemangioma also includes angiosarcoma, which is characterized by the presence of atypical endothelial cells and increased proliferation of vessels. Microvenular hemangioma is distinguished from angiosarcoma by the presence of normal-appearing endothelial cells and the absence of atypical mitotic figures. The clinical course of microvenular hemangioma is usually benign, with slow growth and spontaneous regression. Treatment is often unnecessary, but laser therapy or surgical excision may be considered in selected cases.
small size of circumscribed hobnail hemangioma is of help in the dis-
tinction of both entities, however, there are rare neoplasms showing
overlapping morphological features between both entities (5).

**Retiform hemangioendothelioma**

Retiform hemangioendothelioma (RHE) is a distinctive vascular
neoplasm that arises mainly in the distal extremities of young
adults. Occasionally, it is seen on the trunk, penis, or scalp (7), and
rare cases of multicentric lesions were reported (9). Clinically, RHE
is characterized by an infiltrative growth pattern and a high rate of
local recurrences, but metastasis to a lymph node has only been
seen in one patient so far (7). The morphologic hallmark of RHE is
long, Arborizing, thin-walled vascular spaces that infiltrate in a reti-
form pattern reminiscent of the normal rete testis. The neoplastic
vascular spaces are lined by a single layer of monomorphic hobnail
endothelial cells without prominent atypia and increased mitotic
activity. Solid areas composed of plump oval or polygonal neoplas-
tic cells are often present in deeper parts of lesions, whereas
superficially, dilated vascular structures with intraluminal papillary
projections are infrequently evident. Neoplastic cells are positive
for endothelial markers, but surrounding actin-positive pericytes
are not evident. A prominent lymphocytic infiltrate composed of
mature B and T lymphocytes is present in at least 50% of cases.
The most important differential diagnosis of RHE is aggressive cuta-
neous angiosarcoma, which may show focally, retiform features as
well. However, cutaneous angiosarcoma occurs primarily in the head
and neck region of elderly patients and is characterized by anastomo-
sing and dissecting vascular spaces lined by atypical endothelial
cells that are often arranged in layers and tufts. Malignant endovo-
cular papillary angioendothelioma (Dabska tumor) is a further rare
vascular neoplasm composed of hobnail endothelial cells. Although
described almost 30 years ago (10), it still represents a vascular
lesion which is poorly understood and in which it is difficult to repro-
duce diagnostic criteria. In contrast to the original description, it has
also been reported in adult patients, and a rather benign clinical
behavior has recently been proposed (11). At the moment it seems
that Dabska tumor comprises a morphological spectrum of lesions
showing overlap with retiform hemangioendothelioma (12) and other
vascular entities.

**Kaposiform hemangioendothelioma**

Kaposiform hemangioendothelioma (KHE) is a recently recog-
nized, uncommon vascular neoplasm that occurs most frequently
in neonates and young children and appears as a solitary lesion in
deep soft tissues of the retroperitoneum, chest wall, upper extrem-
ties, and head and neck region (13, 14). More recently, KHE has
also been found in dermal and subcutaneous tissue of adult
patients (15). KHE is sometimes associated with intestinal obstruc-
tion, jaundice or Kasabach-Merritt syndrome, and in rare cases
features of lymphangiomatosis are seen. KHE was regarded as a
low-grade malignant vascular neoplasm because it sometimes pur-
sues an aggressive clinical course. Although KHE is associated
with a relatively high mortality rate, deaths are almost always relat-
ed to locally invasive effects or as a result of bleeding and con-
sumption coagulopathy. To date, no metastasis of KHE has been
recorded, and small and superficially located lesions amenable to
complete surgical excision are characterized by a favorable clinical
course. It seems best to classify KHE as a locally aggressive but
nonmetastasizing vascular neoplasm. KHE is characterized by cel-

dular lobules of neoplastic cells that are separated by fibrous septa.

Within the lobules, short cellular fascicles of spindle-shaped cells
are intertwined with slit-like vascular spaces reminiscent of those
seen in Kaposi’s sarcoma. Ecstatic capillaries lined by flat endothe-

delial cells containing frequently hyaline thrombi are found in the
periphery of some tumor lobules. Occasionally, small nests of
polygonal epithelioid cells are scattered throughout the neoplasms
(15). Immunohistochemical markers confirm the endothelial nature
of the elongated cells that line the narrow vascular spaces, and
intraluminal pericytes that stain positively for smooth muscle actin
are also seen; spindle cells may be positive for CD34 focally. In
adults, KHE has to be distinguished from nodular Kaposi’s sarco-
ma. The lack of a lobular growth pattern and dilated capillaries with
hyaline thrombi in Kaposi’s sarcoma, which is often associated with
chronic inflammatory infiltrate, is of help. In addition, tumor cells in
Kaposi’s sarcoma stain constantly positive for CD34 and are actin
negative. Spindle cell hemangioma (“spindle cell hemangioen-
dotheolioma”) is seen mainly in the distal extremities, and shows his-
tologically a biphasic pattern of cavernous vascular structures and
ramifying vascular spaces associated with bland spindle cells and
scattered epithelioid endothelial cells. In a superficial location KHE
must be distinguished also from tufted hemangioma. Tufted
hemangioma is characterized by an irregular, cannon-ball distribu-
tion of vascular tufts and lacks lymphangiomatous changes (16).

**Polymorphous hemangioendothelioma**

Polymorphous hemangioendothelioma (PHE) is an exceedingly
rare neoplasm that was first described in lymph nodes (17) and
subsequently in extranodal soft tissue (18). In one of the four
patients with follow-up information, local recurrence and pulmonary
metastasis developed, and the patient died. At the moment, PHE
should be best regarded as a vascular tumor of low-grade malig-
nancy. Histologically, PHE is characterized by solid zones of poly-
gonal tumor cells admixed with an angiomatous component showing
clefs and groups of ecstatic vascular spaces lined by plump hobnail
endothelial cells without striking atypia and proliferative activity.
The polygonal cells contain scant cytoplasm and uniform oval or
round nuclei. Neoplastic cells are positive variably for different
endothelial markers. In contrast to spindle cell hemangioma, PHE
does not contain spindle cell fascicles but solid tumor areas. The
absence of epithelioid endothelial cells with characteristic cytoplas-
mic vacuoles as well as the lack of myxohyaline stroma are of help
distinguishing PHE from epithelioid hemangioendothelioma.
Most importantly, PHE must be separated from angiosarcoma and
metastatic carcinoma. Angiosarcoma shows dissecting and anas-
tomosing vascular channels lined by atypical endothelial cells. Special stains and immunohistochemical markers enable the
exclusion of metastatic carcinoma.

**References**

The lesions which have been characterized (or more clearly under-
the distinction of giant cell angiofibroma from solitary fibrous tumor (SFT) and it is arguable that the giant cells and pseudovascular spaces in giant cell angiofibroma represent degenerative features in SFT. However, tumor cells in SFT tend to have more elongated wavy nuclei, and stromal keloid-like or stellate hyalinization is seen. The vascular pattern in SET is most often thin-walled and pericytoma-like.

Cellular angiofibroma

Cellular angiofibroma is a recently described benign vulval neoplasm which clinically is often mistaken for a Bartholin gland cyst (6). It occurs mainly in middle-aged women but comparable lesions have been described in male patients (7). Thus far, in our experience, no case has either recurred locally or metastasized.

Morphologically, cellular angiofibroma is generally a circumscribed neoplasm composed of uniform spindle cells arranged in short, irregularly intersecting fascicles with wispy stromal collagen bundles, numerous small to medium sized blood vessels which often show prominent hyalinization of their walls, and a varying proportion of mature adipocytes. The tumor cells have ill-defined cell borders, pale cytoplasm and oval or fusiform, bland nuclei, thus closely resembling tumor cells of spindle cell lipoma. They stain positively for vimentin and, in a few cases, for CD34 as well. Generally, these neoplasms are cellular and show quite frequent mitoses, but pleomorphism and tumor necrosis are absent. Stromal mast cells are common.

Because of the brisk mitotic activity, examples of cellular angiofibroma may be mislabeled as sarcoma, especially as leiomyosarcoma. However, smooth muscle tumors of the external genitalia have abundant eosinophilic cytoplasm and cigar-shaped nuclei, and they stain positively for myogenic markers. Because of its location, cellular angiofibroma has also to be distinguished from angiofibroma and they stain positively for myogenic markers. Because of its location, cellular angiofibroma has also to be distinguished from angiofibroma and myofibroblastoma, which is much less cellular and composed of rather rounded myoid tumor cells which stain positively for desmin. In contrast to cellular angiofibroma, spindle cell lipoma is more common in male patients and shows a predilection for the neck and upper back region. It typically contains ropey refractile collagen bundles and lacks numerous blood vessels with hyalinized vessel walls; tumor cells in spindle cell lipoma stain consistently for CD34.

Hyalinizing spindle cell tumor with giant rosettes

Hyalinizing spindle cell tumor with giant rosettes is a rather enigmatic lesion, first described by Weiss and coworkers in late 1997 (8), which has been said to resemble low grade fibromyxoid sarcoma. The original report included 19 cases and, since that time, there have been just occasional case reports (9,10), one of which described possible primary lung involvement (10). These lesions affect mainly young to middle-aged adults and present as a deep-seated slowly growing mass with predilection for the limbs. Most examples have measured less than 10 cm in diameter and, although follow-up data are limited so far, only one tumor has recurred locally and none has metastasized.

Grossly these are well-circumscribed, pale firm tumors but histologically they have infiltrative margins. They consist principally of uniform spindle cells with fibroblastic or neural-like morphology arranged in fascicles in a collagenous or myxoid matrix. Large zones of hyalinization are generally present and characteristically these may form nodules, surrounded in rosette-like fashion by more rounded or ovoid tumor cells in axial array. Pleomorphism is minimal and mitoses are scarce. Some cases show osseous or chondroid metaplasia and one case was reported to show transition to a more cellular fibrosarcoma-like pattern (8). Immunostains very often show positivity for variably specific neural crest antigens (S-100 protein, Leu7, neuron-specific enolase) but this has been claimed to be more striking in the rosette-like foci rather than the spindle cell fascicles.

The original authors proposed that this was a variant of low-grade fibromyxoid sarcoma, differing only in the presence of the giant rosettes, and predicted an indolent, potentially metastatic course. My personal experience has been that the spindle cell areas are usually S-100 protein positive and, while accepting that these lesions bear no resemblance to schwannoma or neurofibroma, I wonder if they might represent a form of low grade malignant peripheral nerve sheath tumor. Certainly similar rosettes can be seen in a variety of tumor types and future electron microscopic studies may help to better resolve the nature of these tumors.

Inflammatory myofibroblastic tumor

(inflammatory fibrosarcoma)

The concept of reactive “tumorous” proliferations composed of fibroblasts, myofibroblasts and chronic inflammatory cells grew in popularity following Bahadori and Liebow’s seminal paper on plasma cell granuloma of the lung (11). Subsequently, such lesions were more often referred to as inflammatory pseudotumors or, more recently, as inflammatory myofibroblastic tumors to emphasize their major cellular constituent and, increasingly, to imply that such proliferations may represent benign neoplasms. They have been described in virtually all organs including the mesentery and retroperitoneum (12). In 1991, Meis and Enzinger (13) proposed that, especially in children, at least some of the intraabdominal lesions previously designated as inflammatory pseudotumor actually represent a true sarcoma which they called inflammatory fibrosarcoma. It is my experience that there is sufficient clinicopathological evidence to justify such a designation for at least a small minority of these lesions, but this is a controversial topic.

The originally published clinical data in Meis and Enzinger’s series described 38 cases. These arose predominantly in the mesentery and retroperitoneum of children (median aged 8.5 years), although comparable lesions in adults also occur. Over one-third of patients had multiple tumors. Among 27 patients with follow-up, 10 developed local recurrence (3 repeatedly) and 3 developed metastases. Overall, 6 patients died of their tumor, although interestingly most were adults. Microscopically, these lesions displayed a spectrum of histological appearances which incorporated two major components; plump spindle cells arranged in cellular fascicles or whorls and a prominent infiltrate of plasma cells and some lymphocytes. The spindle cells showed features of fibroblastic and myofibroblastic differentiation and, invariably, at least some showed nuclear irregularity and contained very large nucleoli. A variable number of ganglion-like cells were present. In common with inflammatory pseudotumor, some cases showed areas of myxoid change and/or marked hyalinization of collagen.

It soon became clear, however, that a significant number of pathologists felt uncomfortable with the designation of sarcoma for these lesions. Such concerns were based upon the fact that some examples were histologically indistinguishable from the reactive process, long known as inflammatory pseudotumor, and upon the possibility that so-called metastasis in fact represented multicentricity. This alternative point of view was supported by a large study of 84 cases from Coffin et al. (14). These authors again noted the predilection for children and location within the abdomen, although
they described cases at a wide variety of sites and occurring up to the age of 46 years. Frequently associated anemia was noted, as was the occasional presence of other systemic features such as elevated erythrocyte sedimentation rate or unexplained fever.

From the histologic point of view, Coffin et al. (14) described the three following principal patterns which were commonly intermixed: i) a myxoid fasciitis-like pattern with mixed inflammatory cells; ii) a more cellular pattern resembling fibromatosis or fibrous histiocytoma but with numerous admixed plasma cells; and ii) a hypocellular fibrous pattern resembling scar tissue, in which there were scattered chronic inflammatory cells and sometimes foci of calcification. Because some cases were multinodular, hard to eradicate and sometimes recurrent (approximately 25%), Coffin et al. further reaffirmed their preference for the designation "inflammatory myofibroblastic tumor". They also noted four patients whose tumors regressed spontaneously and two patients who died of uncontrollable local disease. Importantly, they made no mention of nuclear or cytologic atypia in any of their primary lesions and none of their patients developed metastatic disease. They did, however, describe two cases in which local recurrence was associated with the development of areas having histological features of a histiocytold malignant neoplasm. This phenomenon had been described previously in lung lesions by Spencer and conceptually is quite difficult to reconcile with an intrinsically reactive process.

My personal experience of more than 50 cases, based largely on consultation material with no pediatric bias, has revealed the same predilection for anatomic site and an age distribution of 2 months to 79 years, with 40% of cases occurring in patients older than 18. It has seemed to me that at least a minority of cases do show the nuclear atypia described by Meis and Enzinger — and when this is combined with high cellularity, this inevitably raises concern for malignancy. This concern has been substantiated by the development of liver metastases (by all usual criteria) in at least two patients (both children) and I am aware of other convincing clinically malignant cases in other people’s practices. Admittedly, this is a very small number of “malignant” examples and the majority of other cases are cytologically bland, more closely resembling either fasciitis or the old-fashioned inflammatory pseudotumor.

Given this premise, are there any reliable histological features which allow accurate recognition of inflammatory fibrosarcoma from among the group of inflammatory myofibroblastic lesions as a whole? The major discriminant feature employed by Meis and Enzinger was that of nuclear atypia. In my experience, focally, there may also be very cellular, fascicular areas. Undoubtedly, reliable distinction (in prognostically useful terms) is very difficult but consideration of the nuclear detail of such tumors perhaps allows recognition of a more aggressive subset. Limited available cytogenetic data have revealed a variety of clonal aberrations in lesions of this type (15, 16), supporting their neoplastic nature, and the original protagonists in the dispute concerning the nature of these lesions have very recently moved towards a consensus viewpoint that they should all be regarded as low-grade sarcomas (17, 18).

Principal considerations in the differential diagnosis include fasciitis-like proliferations, fibromatosis, deep fibrous histiocytoma and inflammatory leiomyosarcoma. Some of the fasciitis-like lesions reported at visceral locations may in fact belong in the inflammatory myofibroblastic tumor category — but most cases show much less pronounced inflammation, a more tissue culture-like cytomorphology and they are generally smaller in terms of lesional size. Fibromatosis is more uniformly fascicular, generally lacks any significant degree of inflammation and very rarely has such plump nuclei with prominent nucleoli. Deep benign fibrous histiocytoma is an uncommon lesion and is especially rare in the abdomen or in children. It has a storiform rather than fascicular pattern and usually consists of a highly cellular admixture of short fibroblast-like cells and plumper histiocyte-like cells. Chronic inflammatory cells are relatively sparse. Inflammatory leiomyosarcoma is more cellular and more cytologically atypical than inflammatory myofibroblastic tumor and generally shows much more extensive actin immunostaining. Lymphocytes typically predominate in the inflammatory infiltrate.

**Low-grade myofibroblastic sarcoma**

For many years, the existence of myofibroblastic neoplasms (and especially myofibroblastic sarcomas) has been disputed, principally because the scientists who described this cell type felt strongly that this was not possible (19). Yet one of the prototypical myofibroblastic lesions, desmoid fibromatosis, is now known to be a clonal proliferation and a wide variety of benign neoplasms have been shown to have a myofibroblastic phenotype at the immunohistochemical and ultrastructural levels (e.g., infantile digital fibromatosis, intranodal myofibroblastoma, mammary myofibroblastoma and angiomylipoblastoma). It has also become evident that a variety of more aggressive lesions show myofibroblastic differentiation, including inflammatory myofibroblastic tumor (also known as inflammatory fibrosarcoma), infantile fibrosarcoma and some cases of so-called “MFH” (20). To this list has been added more recently a distinctive group of lesions which we have designated as low-grade myofibroblastic sarcoma (21).

Low-grade myofibroblastic sarcoma (21) affects adults of either sex over a wide age range, with a peak incidence between the ages of 20 and 50. Overall anatomic distribution is wide but, strikingly, around 25% of cases occur in the oral cavity (especially the tongue). Most cases present as slowly growing perifascial or deep-seated masses which generally measure less than 5 cm (with larger exceptions). Although follow-up data are limited at present, local recurrence is a feature of 20-30% of cases (usually due to marginal or incomplete excision), and occasional patients develop indolent metastases.

Grossly, most lesions are firm, pale and fibrous with infiltrative margins, reminiscent of desmoid fibromatosis. Generally there is no hemorrhage or necrosis. Most cases are hypercellular throughout, usually being more cellular than a fibromatosis and, distinctively, these lesions typically show a diffusely infiltrative growth pattern within skeletal muscle (producing a pattern rather reminiscent of proliferative myositis). Focal storomal hyalinization is common. Tumor cells show usual myofibroblastic features, with variably wavy/tapering or plump/vesicular nuclei, and typically are arranged in a fascicular pattern. When compared to a fibromatosis there is distinctly more nuclear atypia, even if only mild and focal in extent. Scattered multinucleate tumor giant cells are occasionally seen and, in most cases, the mitotic rate does not exceed 5 per 10 high-power fields. Immunohistochemically around 65% of cases show diffuse desmin immunopositivity and a similar proportion of cases (although not necessarily the same ones) are smooth muscle actin positive. Electron microscopy shows typical myofibroblastic features.

Low-grade myofibroblastic sarcoma should be distinguished from fibromatosis, myofibromatosis, solitary fibrous tumor, other types of myofibroblastic sarcoma, fibrosarcoma and leiomyosarcoma. The fairly consistent hypercellularity and at least focal nuclear
atypia excludes fibromatosis, while myofibromatosis typically has a distinctive biphasic growth pattern with primitive pericytoma-like areas and myoid nodules or whorls (which are often hyalinized). Solitary fibrous tumor is well circumscribed, has a patternless architecture and is generally immunonegative for myogenic markers. Fibrosarcoma has paler (less eosinophilic) cytoplasm and lacks immuno or EM evidence of myoid differentiation. Leiomyosarcoma usually has more circumscribed margins, more eosinophilic cytoplasm and more cigar-shaped nuclei.

Sclerosing epithelioid fibrosarcoma

Sclerosing epithelioid fibrosarcoma, first described by Meis-Kindblom and colleagues from AFIP in 1995 (22), is an uncommon and probably poorly recognized type of sarcoma which has only slowly gained acceptance as a distinct entity. In part, this reflects the considerable morphological overlap between this and other tumor types, but the recent publication of additional cases (23, 24) is indicative of justifiably increasing recognition. These tumors affect mainly young to middle-aged adults of either sex, who present usually with a deep-seated mass in the lower limb, limb girdle or trunk. Almost all cases measure less than 10 cm in diameter and the growth rate is variable. Approximately 50% of patients develop local recurrence and/or distant metastasis, but systemic spread is usually delayed for 5 years or more.

These are generally well circumscribed, lobulated, rubbery masses which histologically are notably hypocellular with extensive stromal hyalinization. However, the cellular areas consist of nests, cords and strands of relatively small epithelioid cells which most often have clear cytoplasm. Other areas may have an alveolar growth pattern but, in addition, there are generally areas with a fascicular spindle cell appearance reminiscent of conventional fibrosarcoma. The densely hyaline stroma may simulate osteoid and there is often a pericytoma-like vascular pattern. Pleomorphism is minimal and mitoses often do not exceed 5 per 10 mean power frequencies. Published immunophenotypic findings (as well as personal experience with cases of this type) have been variable but it seems that at least some cases stain positively for epithelial membrane antigen and less often for keratin and S-100 protein. Ultrastructural studies have shown fibroblastic features and recent cytogenetic data in one case (25) showed nonspecific clonal aberrations.

The differential diagnosis includes principally metastatic carcinoma, ossifying fibromyxoid tumor, osteosarcoma and monophasic synovial sarcoma. In general, the combination of clinical context, focally distinctive cytoarchitectural features and careful use of immunohistochemistry resolve this problem so long as one is aware of the existence of this unusual tumor.

References