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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. Ulceration 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 0D34 (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 shealth 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 rabdoid 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 hematoma or Kaposi's sarcoma. 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 calcitication 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 subtascial 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 cytomorphology, 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 (GEAP). 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 plasmacytoid 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.

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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 differentiation. 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 sott 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 11 p15, 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-POR 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 consistentt(11;22)(p13;qP2) 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 consistently includes 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 (013) 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-FLI1* 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.

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