

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 S100 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 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)(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-PCR 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;p12) 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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## 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 irregular anastomosing vascular spaces, plasma cells and hyaline globules is of help in the distinction of microvenular hemangioma. Anastomosing neoplastic vascular structures in aggressive cutaneous angiosarcoma are lined by atypical endothelial cells. In addition, no biphasic proliferation of CD31+ endothelial cells and actin-positive pericytes is evident in angiosarcoma. Further differential

diagnoses include rare tufted hemangioma and "targetoid hemosiderotic hemangioma" (see below).

### Hobnail hemangioma ("targetoid hemosiderotic hemangioma")

Hobnail hemangioma is a further recently recognized benign vascular lesion. The original term "targetoid hemosiderotic hemangioma" resulted from the characteristic targetoid clinical appearance (4). Further expanded clinicopathological studies have shown clearly that most vascular lesions showing histological features of this distinctive neoplasm lack this clinical appearance, which is also evident in other conditions (5, 6). In order to emphasize the independent diagnostic hobnail cytomorphology of the targetoid appearance is evident, the alternative term of hobnail hemangioma was proposed (5, 7). Hobnail hemangioma represents a superficially located lesion in which a broad spectrum of diagnoses is suggested clinically, ranging from dermal melanocytic nevus and hemangioma to fibrous histiocytoma (6). It affects mainly adults with a slight male predominance; most common anatomic locations are the extremities and the trunk (6), and rare cases were reported in the head and neck region (5, 8). Diagnostic criteria of hobnail hemangioma are a biphasic growth pattern (dilated vascular spaces on the surface and more narrow vascular spaces infiltrating deeper parts of the dermis) and a hobnail cytomorphology of neoplastic endothelial cells (plump and prominent cells with scanty, ill-defined cytoplasm and large, mostly hyperchromatic nuclei). Further features include an associated lymphocytic infiltrate, fibrosis of the dermal collagen and hemosiderin deposits. These morphological features vary according to the age of the neoplasm. More mature examples are composed predominantly of narrow vascular structures, and in few cases overlapping features to retiform hemangioma (see below) were noted (5). In contrast, "early" examples of hobnail hemangioma are mainly composed of dilated vascular structures in the upper dermis resembling features of early Kaposi's sarcoma and lymphangioma (4, 6). Immunohistochemically, endothelial cells stain positively for CD31, whereas CD34 stains only a minority of cases (6). In contrast to other benign neoplasms of blood vessels, neoplastic vascular structures are not surrounded by a complete layer of actin-positive pericytes (5, 6). Furthermore, a limited number of cases stained positively for vascular endothelial growth factor receptor (VEGFR-3) (6), a recently described marker of lymphatic endothelial cells. These results and the evidence of associated lymphocytes and the described morphological features suggest a lymphatic line of differentiation of neoplastic cells in hobnail hemangioma (6). Despite the bland clinical picture, hobnail hemangioma may show worrisome histological features and the diagnosis of patch- or lymphangioma-like Kaposi's sarcoma, well-differentiated angiosarcoma, and retiform hemangioma is suspected. In addition to different clinical features of evolving Kaposi's sarcoma, hobnail hemangioma is characterized by a biphasic growth pattern and hemosiderin deposits. Early examples of Kaposi's sarcoma are seen in the reticular but not in the papillary dermis, show an adnexocentric growth and frequently contain plasma cells. Cutaneous angiosarcoma occurs mainly in the head and neck region of elderly patients, and is characterized morphologically by anastomosing vascular structures lined by atypical and proliferative active endothelial cells. Low-grade malignant retiform hemangiomaendothelioma presents clinically usually as an exophytic or plaque-like vascular tumor and is characterized by a high rate of often repeated local recurrences (7). The