Rev Esp Patol 1999; Vol. 32, Nº 3: 271-282
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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).

Table 1. Specific (primary) chromosome changes in adipocytic tumors.

Ordinary lipoma	t with 12q13-15 t with 6p21 -23 t with 11q13
Rearrangement involving 1p36.1 -36.3	
Lipoblastoma	t with 8q1 1-13
Hibernoma	t with 11q13,10q22
Spindle cell and pleomorphic lipoma	Loss of 16q13-qter Unbalanced aberration of 13q
Atypical lipoma/ well-differentiated liposarcoma	+ Ring or long marker (sequences 12q1 3-qi 5)
Myxoid and round cell liposarcoma	t(12;16)(q13;p11) t(12;22)(q13;q11)
Pleomorphic liposarcoma	Complex rearrangements

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 a 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); neurofibroma (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 tapering or wavy spindle cells featuring perivascular accentuation of cellularity and focal S-100+ immunoreactivity in about 50% of cases); and, well-differentiated scierosing 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 unrelated 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), scierosing 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 kayotypically. 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 occur 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 22q1 2. 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). It often presents clinically as a dome-shaped or polypoid 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, scierosing, 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, ii) pleomorphic liposarcoma, characterized by complex karyotypes. Rarely, liposarcoma may combine features of different histological subtypes.

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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.