REVIEW ARTICLE

Soft Tissue Tumors

New Perspectives on Classification and Diagnosis

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SUMMARY

Background: In recent years, new tumor entities have been described and previously known tumor types have undergone a reassessment. This article offers an overview of recent developments in the classification and interpretation of soft tissue tumors.

Methods: Selective review of publications from 1990 until 2008 from the literature database of the Consultation and Referral Center for Soft Tissue Tumors in Jena. The current status of the classification and morphological diagnosis of these tumors is described.

Results: The description of the biological behavior of soft tissue tumors has become more detailed with the introduction of two intermediate categories ("intermediate, locally aggressive" and "intermediate, rarely metastasizing"). There have also been some changes in terminology.

Previously established terms such as "malignant fibrous histiocytoma" or "hemangiopericytoma" will be used much less often in future, because these tumor types have been reinterpreted. The WHO recommends that highly differentiated liposarcoma be renamed "atypical lipomatous tumor." Molecular diagnostic techniques have become firmly established as an ancillary diagnostic method. The importance of molecular tumor characterization for individually tailored therapy is already becoming clear.

Conclusions: Optimal diagnosis is the prerequisite for effective therapy and can be achieved only with state-of-the-art knowledge of the pathology of soft tissue tumors.

Key words: soft-tissue sarcoma, biopsy, cancer diagnosis, molecular biology, molecular medicine

Soft tissue tumors belong to a group of neoplasms that can cause particular problems in their diagnosis and/or treatment. Because they are relatively rare, the individual physician usually has limited experience of these tumors. To make things worse, there is an astonishing variety of morphological types and subtypes. In addition, it always has to be borne in mind that these tumors can be heterogeneous: the smaller the biopsy sample, the more likely it is that only a temporary, working diagnosis is going to be possible. This is of course particularly true of a purely cytological examination, since this can only evaluate individual cells. Nevertheless, in the hands of an experienced investigator, the cytological findings can in most cases provide a result that is usable for clinical purposes. Valid conclusions can frequently be drawn not only about the malignancy of the tumor, but also about its classification.

Biopsy is an essential component of the preoperative diagnostic work-up and should be carried out in every case in which malignancy is suspected. Moreover, this is the only way to establish whether a soft tissue tumor is malignant, and this confirmation is a prerequisite for any neoadjuvant therapy.

The classification of neoplasms of the soft tissues, like that for other tumors, is not static. New aspects or interpretations, once validated, have to be taken into account and incorporated into clinical practice. From time to time, therefore, it becomes necessary to update the tumor classification, modify it, or even alter major parts of it. This was last done for soft tissue tumors by the World Health Organization (WHO) in 2002 (1). The present paper will describe important new aspects relating both to the assessment of malignancy and to the deletion of established diagnostic terms and the introduction of new ones. It does not, however, aim to go into the individual details of all the new morphological entities, such as tumors of the perivascular epithelioid cells ("PEComas") (2). That would be beyond the scope of a review article. In addition, a short overview of the new methodological focuses of morphological diagnostic techniques will be given.

Methods

The basis for this description of the present status of the classification and interpretation of soft tissue tumors is the current WHO classification. The personal experiences of the authors in their work at the Consultation and Reference Center for Soft Tissue Tumors (Konsultations- und

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Referenzzentrum für Weichgewebstumoren) inform the review; the relevant literature from the period 1990–2008 was retrieved from the data bank of this center.

Results

Soft tissue tumors are classified according to their similarity to normal tissue; that is, the designation of the tumor reflects the tissue of which it is a tumorous imitation. Features of cell differentiation are especially important; features of tissue architecture also have a place. Thus, the current WHO classification includes adipocytic tumors, fibroblastic/myofibroblastic tumors, fibrohistiocytic tumors, tumors of smooth muscle and skeletal muscle, pericytic tumors, and vascular and chondro-osseous tumors. Neoplasms for which there is no known comparable normal tissue are grouped together in the last group of tumors of uncertain differentiation. This group is now much larger than before; it includes, for example, synovial sarcoma, which neither arises in a synovial membrane (indeed, a direct association with the joint lining is regarded as notably exceptional) nor shows the differentiation features of such a membrane.

Extension of statements about biological behavior

Tumors are basically divided into the benign and the malignant. Clinical practice has shown, however, that this strict dichotomization can be problematic, because it can in some circumstances give too imprecise a description of the actual behavior of the tumor. Thus, it is generally accepted today that there is a biological continuum with intermediate forms between the extremes of "benign" and "malignant," and this applies to soft tissue tumors as much as to others. The concepts of "intermediate malignancy" or "borderline malignancy" are known from other tumor families. In view of this development, it is interesting that classical German pathology included the concept of "semimalignancy," a term used to describe tumors with locally malignant behavior but lacking the potential to metastasize.

For soft tissue tumors, to allow more detailed statements about their biological behavior, the current WHO classification introduced an intermediate biological category between the definitely benign and the definitely malignant. This was then further subdivided into "intermediate, locally aggressive" and "intermediate, rarely metastasizing." As a guide, for inclusion in the latter category, metastasization should take place in fewer than 2% of cases. The locally aggressive group includes, for example, superficial and deep fibromatosis. The intermediate tumors, which normally have a benign course but can occasionally lead to metastases, include solitary fibrous tumor, inflammatory myofibroblastic tumor, and angiomatoid fibrous histiocytoma. Strictly speaking, the cutaneous fibrous histiocytomas, deep fibrous histiocytomas, and diffuse tenosynovial giant cell tumors, which are generally regarded as benign, ought to be included in this category, for in extremely rare cases metastases are possible with these neoplasms as well (3, 4).

The likelihood that a malignant tumor will metastasize

can be determined by its degree of malignancy. In Germany the French FNCLCC grading system (Fédération Nationale des Centres de Lutte Contre le Cancer) has become generally used. This system determines malignancy by a scoring system that takes account of mitotic activity, any necrosis, and tumor differentiation. The total score gives the malignancy grade. However, not all sarcomas can be equally well assessed by this grading scheme. Some sarcomas have in addition a fixed malignancy grade, while for others (e.g., epithelioid sarcoma, clear cell sarcoma, or alveolar soft part sarcoma) grading is impossible or meaningless, because it bears no relation to the true course of the disease. Despite this, however, one ought in general to grade neoplastic malignancy using this schema. The malignancy grade identifies not just the patients at highest risk of metastasis, but also those who would benefit most from adjuvant therapy. In addition, malignancy grading is absolutely essential if the results of clinical studies are to be comparable.

Examples of new interpretations of hitherto established entities and changed terminology

The tumor known hitherto in clinical practice as highly differentiated liposarcoma, which accounts for 40% to 45% of all liposarcomas, which in their turn make up around 20% of sarcomas in adults, is no longer listed as a sarcoma in the 2002 WHO classification. These tumors never lead to metastases, and for this reason they have been reclassified into another category (intermediate, locally aggressive). As a diagnostic term, "atypical lipoma" (when in the superficial soft tissue) or "atypical lipomatous tumor" (when located in the deep soft tissue) is recommended. This captures the fundamental criterion that distinguishes this tumor from benign lipoma, which consists in the presence of atypia of the adipocytic tumor cell nuclei and also of cell nuclei in the stromal tissue, and avoids the term "sarcoma" (5). The term "highly differentiated liposarcoma" can of course still be used as a synonym. To avoid terminological confusion in everyday diagnostic practice, however, it is essential that clinicians and pathologists agree on the nomenclature to be used and on its diagnostic implications.

The suggested name change to "atypical lipomatous tumor" applies to all highly differentiated liposarcomas of the deep peripheral soft tissue (as in the extremities or trunk), because in these locations the tumors can be curatively treated by excision with a margin of healthy tissue and the patient is then cured. The situation is different when similar neoplasia develop in the mediastinum or retroperitoneal region, where in many cases extirpation including enough normal tissue is unachievable, and therefore repeated, and in the end unconquerable, local recurrences may occur. Such tumors can have a fatal course even without the ability to metastasize, so that for them the term "liposarcoma" continues to be preferred. The tumors described synonymously as "highly differentiated liposarcoma" or "atypical lipomatous tumor" can, by the way, acquire metastatic potential if they dedifferentiate, if a non-lipogenic (usually highly

Figure 1:

Atypical lipomatous tumor: adipocytes of varying size with marked nuclear atypia

Figure 2:

Dedifferentiated liposarcoma: alongside structures of an atypical lipomatous tumor, formations of an undifferentiated spindle cell sarcoma are seen

malignant) sarcomatous part develops within the well-differentiated lipoma. Such neoplasms are uniformly known as dedifferentiated liposarcomas and are unequally malignant (6) (*Figures 1 and 2*).

Malignant fibrous histiocytoma (MFH) has already been the subject of debate as a tumor entity for some time (7), after it became regarded in the 1970s and 1980s, when the term became established, as the most common soft tissue tumor of advanced adulthood (8). The original assumption that this was a tumor of histiocytes that possessed the ability to modulate into facultative fibroblasts could not be confirmed. Rather, it was shown that the phenotype of the most common subtype, "pleomorphic MFH," can be adopted by various soft tissue tumors in a framework of a loss of differentiation (9)—i.e., that in many cases there is no independent entity and the cells of this tumor are basically dedifferentiated or undifferentiated. Modern morphological investigation techniques are increasingly making it possible to remove the defined soft tissue tumors from the group of so-called MFHs by demonstrating the existence of residual differentiation. The remaining tumors—the pleomorphic, malignant fibrous histiocytomas in the narrower sense—

should, according to the recommendations of the WHO, better be described as "undifferentiated pleomorphic sarcomas" that cannot be further subtyped. Today they make up no more than 5% of sarcomas in adults.

The subtype of malignant fibrous histiocytoma identified as the second most common was the myxoid variant (10). As the tumor cells are now understood as fibroblastic cells, the preferred designation today is "myxofibrosarcoma"—a term first used in 1977 by Angervall et al. (11). This tumor is the most common soft tissue sarcoma seen in older adults.

The concept of hemangiopericytoma rests on the postulate that the tumor cells derive from pericytes and are pericytically differentiated. This is incorrect: in the first place, various "nonpericytic" tumors can give a good imitation of the appearance of a hemangiopericytoma, and in the second place, even the cells of the so-called hemangiopericytoma in the narrower sense are not pericytically differentiated, but obviously fibroblastic in nature (12). As a logical consequence, hemangiopericytoma has been taken out of the group of pericytic (perivascular) tumors and integrated into the family of fibroblastic/myofibroblastic tumors. Moreover, a development may be anticipated that will see its elimination as a diagnostic term (and indeed to a large extent already has done): hemangiopericytoma of the soft tissues is now a part of the family of solitary fibrous tumors (SFT) (13, 14). Like the hemangiopericytomas originally, soft tissue SFTs are of intermediate malignancy. Usually they have a benign course, but in rare cases which generally cannot be predicted on the basis of the histological features, they can metastasize.

Molecular diagnosis of soft tissue tumor pathology

The diagnosis of soft tissue tumors (histological classification and, if malignant, the malignancy grade) is done principally on the basis of the hematoxylin-eosin (H & E) section. Despite the enormous increase in additional methods available, the H & E section remains the gold standard of morphological diagnosis to this day. With regard to the classification, when necessary (nowadays as a matter of routine) immunohistochemical tests are done, which are used to identify cell line differentiation or an antigen pattern typical of the diagnosis (15).

Over the past 20 years, methods of genetic analysis have also increasingly been opened up to allow the identification of chromosomal translocations, deletions, and amplifications in the diagnosis. Molecular pathological methods are employed for diagnosis particularly when no tumor classification is possible on the basis of either the H & E section or the additional immunohistochemical tests (16). In everyday diagnostic practice two main techniques are used to demonstrate chromosomal translocations, both of which can be used on tumor tissue that has been routinely embedded in paraffin. With one of them, the chromosomes, or fragments of chromosomes, can be marked in the interphase nucleus and thus be examined directly (through

fluorescence in situ hybridization, FISH), while with the other the product generated by gene fusion (hybrid RNA) can be shown by means of reverse transcription polymerase chain reaction (RT-PCR). The latter has the advantage of demonstrating not only the translocation, but also the sites of the breakpoints in the genes. Numerous translocations with diagnostic relevance are known at the present time; a small fraction of them are shown in the *Table* together with the resulting fusion genes. Although it was first believed that the translocations were each specific for a particular type of tumor, it is now understood that this is not always necessarily the case. Chromosomal translocations are not always diagnostically unambiguous (17).

An example of the diagnostic relevance of chromosomal amplifications is provided by certain lipomas. The atypical lipomatous tumor (synonym: highly differentiated liposarcoma) is characterized karyotypically by ring chromosomes and giant marker chromosomes. This naturally leads to the appearance of multiple copies of the genes located on these chromosomes, such as the MDM2 and CDK4 genes. This can be demonstrated, in many cases also through the use of antibodies against the synthetic products of these genes, which are present in greater quantities and can thus be shown immunohistochemically (18).

However, not all soft tissue tumors show consistent translocations that can be used for classification. Another interesting application of molecular diagnostic techniques is in the gene expression analysis of these tumors. By means of the definition of expression clusters in established soft tissue tumors, at least some tumors that are phenotypically and immunohistochemically ambiguous can be assigned to particular tumor families. This method has been successfully tested, for example, in so-called pleomorphic malignant fibrous histiocytomas (undifferentiated pleomorphic sarcomas), where further indications were derived that most of these tumors represent a loose collection of dedifferentiated soft tissue tumor entities (19).

Molecular diagnostic techniques as the starting point for new therapeutic approaches

The aim of optimized therapy of neoplastic disease is to tailor treatment to the individual tumor. The molecular characterization of a malignant soft tissue tumor can give an indication of how to influence its biological behavior in a targeted way. The treatment should inhibit growth of the tumor; if possible, it should also prevent metastasis or eliminate already existing metastases. A good example is the most frequent mesenchymal tumor of the gastrointestinal tract, gastrointestinal stromal tumor (GIST). With these tumors, an activating mutation of the KIT gene (rarely, of the PDGF-receptor- α gene) is regularly present, leading to heterodimerization and also immunohistochemically measurable overexpression of the corresponding growth factor receptors (20). These receptors are tyrosine kinases. In patients with nonresectable, metastasizing GISTs, which are usually resistant to radio- and chemotherapy, it is possible

TABLE

Chromosomal translocations in malignant soft tissue tumors

Soft tissue sarcoma	Translocation	Gene fusion product
Alveolar rhabdomyosarcoma	t (2;13) (q35;q14)	PAX3-FKHR
Alveolar soft part sarcoma	t (X;17) (p11;q25)	ASPL-TFE3
Clear cell sarcoma	t (12;22) (q13;q12)	EWS-ATF1
Dermatofibrosarcoma protuberans/ giant cell fibroblastoma	t (17;22) (q21;q13)	COL1A1-PDGFB
Ewing sarcoma/PNET	t (11;22) (q24;q12) t (21;22) (q22;q12)	EWS-FLI1 EWS-ERG
Infantile fibrosarcoma	t (12;15) (p13;q26)	ETV6-NTRK3
Myxoid/round cell liposarcoma	t (12;16) (q13;p11)	FUS-CHOP
Synovial sarcoma	t (X;18) (p11.2;q11.2)	SYT-SSX1 SYT-SSX2

PNET, peripheral/primitive neuroectodermal tumor

to make use of this knowledge and give the patient tyrosine kinase inhibitors. These drugs inhibit ATP binding of the receptors and thus their enzymatic activity, and thus also inhibit receptor-mediated growth stimuli. It may be assumed that GISTs will respond to this kind of therapy in up to 80% of cases, have their growth inhibited, and will shrink. The molecular characterization of a GIST will also give information about which drug works best, and the effective dosage. New tyrosine kinase inhibitors now exist that are particularly effective in the case of exon 9 mutations.

It is to be hoped that comparable drugs will increasingly become available or be developed for other soft tissue tumors. First approaches for extraskeletal myxoid chondrosarcoma are promising (21).

Conflict of interest statement

The authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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