THE EVOLUTION OF SOFT TISSUE TUMOUR TAXONOMY:
WHAT STILL NEEDS TO BE DONE?

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Bullet points:

- There has been progressive improvement in soft tissue tumor classification schemes over the past 20-30 years, but problems remain.
- Some outdated diagnostic concepts need to be abolished (e.g. MFH) or substantially revised or redefined (e.g. hemangiopericytoma and adult-type fibrosarcoma).
- Some tumor nomenclature is illogical or misleading and may need to be reappraised (e.g. synovial sarcoma and extraskeletal myxoid chondrosarcoma).
- Classification among the broad group of vascular tumors is hampered by our lack of understanding regarding pathogenesis, line(s) of differentiation and biologic status/potential.
- The impact of genetic analysis has been positive, but, as more data emerge, the results pose challenges for both morphologic and molecular classification schemes.
INTRODUCTION

For many years, classification schemes have provided very important underpinnings in the diagnosis, clinical management and research of human tumors. Furthermore, the trend towards the development of widely accepted consensus classification schemes, both within individual subspecialty groups (e.g. hematopathology) or more broadly by the World Health Organization (WHO), have helped greatly to ensure more reproducible diagnosis across larger national and international patient groups, thereby enabling more effective and meaningful analysis of both clinical and more basic research studies, while also allowing more accurate interpretation of clinical trials data.

In this regard, the classification of soft tissue tumors has made very substantial steps forward in the past 20-30 years, based upon the gradual introduction of more reproducible and objective diagnostic criteria (often facilitated by immunohistochemistry), the arrival of cytogenetic and molecular genetic data which have in large part further facilitated objectivity, as well as a willingness to question poorly substantiated dogmas based on limited data combined with the recognition that ‘histogenesis’ has very little meaning in the context of mesenchymal neoplasia. In purely pragmatic terms, the modern classification of these lesions is now largely based on evidence of a specific line of differentiation or else on genotypic data. In some tumor types (e.g. rhabdomyosarcoma), classification is based on a combination of these approaches but it is also worth noting that a remarkable proportion of the tumors in which we have no real understanding of the precise line of differentiation (for example, alveolar soft part sarcoma, synovial sarcoma and desmoplastic small round cell tumor), can be sharply and strictly defined by their karyotype and related fusion gene(s).

The 2002 WHO Classification took major steps in better defining biologic potential (benign, intermediate locally aggressive, intermediate rarely metastasizing and malignant), even acknowledging that occasional benign tumors may give rise to distant metastasis, and “grasped the nettle” in terms of allocating more tumors to the category of uncertain differentiation and acknowledging that so-called ‘malignant fibrous histiocytoma’ is not a definable entity. However, there do remain nosologic problems, uncertainties and contradictions in the current classification of soft tissue tumors which will need to be addressed in the years to come. The aim of this brief overview is to highlight some of these areas.
OUTDATED DIAGNOSTIC CONCEPTS

Changes in nomenclature, particularly if the terms in question have been used for many years, are painful and often resisted for no clear reason other than ‘discomfort’ or the false belief that retaining outdated terminology will continue to be of value to non-specialist colleagues, especially clinicians. However, such resistance is not intellectually rigorous, particularly if there are extensive data to support more logical alternatives. Several such areas will need to be addressed in any future classification scheme, primary examples among which are as follows:

1. Since it is now generally accepted that the majority of pleomorphic sarcomas can be meaningfully subclassified and that such subclassification has clinical and prognostic relevance, then there really is no justification for retaining the term ‘malignant fibrous histiocytoma’ (MFH) in any future classification scheme since the pleomorphic, giant cell and inflammatory variants are not definable or reproducible entities. The so-called myxoid and angiomatoid subsets undoubtedly represent discrete tumor types, better allocated to the fibroblastic and uncertain differentiation categories, respectively. The 2002 WHO Classification paved the way for this change, in explaining the largely meaningless nature of the ‘MFH’ terminology;

2. For very similar reasons, since it is now recognized that the large majority of lesions formerly classified as so-called hemangiopericytoma in fact have nothing whatever to do with pericytes (most of them representing solitary fibrous tumours), then, since we now have a more sharply defined group of pericytic neoplasms, presently known as myopericytomas (until such time as the loosely used term ‘hemangiopericytoma’ can be more meaningfully applied), then a case could be made for dropping use of the term ‘hemangiopericytoma’, at least for the foreseeable future;

3. While it is clear that there is a group of sarcomas which show fibroblastic differentiation (foremost among which are myxofibrosarcoma and low-grade fibromyxoid sarcoma), the concept of ‘adult fibrosarcoma’ as used in the past, defined by high cellularity and a herringbone growth pattern, for all practical purposes seems not to exist, other than as a pattern of dedifferentiation in dermatofibrosarcoma protuberans (DFSP). The overwhelming majority of tumors which would have been classified as adult-type fibrosarcoma in years gone by would nowadays be classified more meaningfully as either monophasic synovial sarcoma or malignant peripheral nerve sheath tumor. The process
of dropping this terminology, in large part, has already happened through a process of attrition, but a more stringent and meaningful re-definition of fibroblastic sarcomas in adult patients would be very useful going forward.

NOMENCLATURAL ANOMALIES

Whether or nor to address the issue of tumors with inappropriate names is more of a nebulous problem, insofar as there are good arguments, for example, that the concept of ‘synovial sarcoma’ is meaningfully defined and understood both in the research and clinical arenas, even if we fully understand that these tumors have nothing whatever to do with synovium. Nevertheless, such classificatory feebleness would likely not be tolerated in other areas of science and arguments, now 25 years old, that these lesions would better be classified as ‘carcinosarcomas’ of soft tissue may ultimately prevail and would certainly be easier to defend. Other examples which might be easier to address, in that they would likely have less direct clinical or practical impact, include extraskeletal myxoid chondrosarcoma, which is now well understood to have nothing whatever to do with cartilage and so-called angiomatoid ‘MFH’, which bears no relationship to the formerly popular category of ‘fibrohistiocytic’ tumors but which is undoubtedly a discrete and now genetically well-defined tumor type. One could also make a case that the term ‘hemangioendothelioma’ needs to be more sharply refined in the future, since tumors within this category, which have often been lumped together as being of ‘intermediate’ or ‘borderline’ biologic potential, in fact span a substantial spectrum of clinical behavior – thus refinement of these terms would likely facilitate greater clinical understanding.

LACK OF BIOLOGIC UNDERSTANDING

Vascular lesions represent an area in which there is substantial uncertainty and ambiguity as to the manner in which these lesions develop, whether or not there is any significance to designating them as hemangiomas or malformations and whether or not there is any importance in determining whether these lesions show blood vascular or lymphovascular differentiation. At the present time, some of these questions are likely unanswerable. While intuitively we tend to think of vascular tumors which are composed of mixed vessel types, including larger specialized vessels such as veins and arteries, as being malformations or ‘hamartomas’, there really is no rational basis for this belief, particularly since these tumors may develop at any age and they
often show a propensity for persistent/recurrent growth. Furthermore, the development of larger more specialized vascular structures is only the morphologic counterpart of very well-differentiated lesions composed of mixed cell types in other organ systems, such as pulmonary ‘hamartoma’ and Peutz-Jegher polyps, both of which are now regarded as clonal neoplastic processes. There is some sense that classification of vascular lesions is increasingly based on clinical and behavioral parameters, rather than morphology, but the former are very poorly reproducible and this is an area which is beginning to give an impression of ‘witchcraft’. Part of the problem in this regard likely relates to the fact that there are few, if any, genetic data regarding most types of benign vascular lesion, combined with the fact that clonality *per se* is no longer regarded as being definitional for a neoplastic process. Similarly, the long-standing importance which has been attached to distinguishing between blood vascular and lymphovascular lesions seems quite illogical not only because daily experience demonstrates that many vascular lesions contain vessels of both types but also, given that lymphatics develop from the venous system during embryogenesis, then it is hardly surprising if there may be substantial overlap in the phenotype of these vessels. At the present time, however, progress in this area is likely to be slow while available data are so limited and controversial.

**THE IMPACT OF GENETICS**

There is no question that the development of cytogenetic and molecular genetic technologies, as applied to soft tissue tumors, has had enormous impact in advancing both classification and understanding of these diseases – outstanding examples, among others, include the proof that biphasic and monophasic synovial sarcoma represent variants of a single entity, that the embryonal and alveolar subtypes of rhabdomyosarcoma are biologically and prognostically quite distinct, that Ewing’s sarcoma, peripheral primitive neuroectodermal tumor and peripheral neuroepithelioma are all essentially a single entity and, similarly, that the myxoid and round cell variants of liposarcoma are phenotypic variants of a single tumor type. Increasingly, arguments are made that molecular genetic classification should supercede morphologic or phenotypic classification and such an approach is becoming the standard of care in large areas of leukemia diagnosis and therapy. However, as more data are gathered, areas of confusion are also beginning to appear, which may complicate the clinical utility of this technology, at least in the short term. Examples both in favor and against the greater use of
genetic data in determining classification that may help to provoke discussion in this area are as follows:

1. It is recognized that there are variably subtle but undoubted morphologic similarities between spindle cell lipoma, mammary-type myofibroblastoma and cellular angiofibroma – yet these lesions each retain clinical or phenotypic differences. However, data are now emerging that all of these lesions share the same underlying genetic signature, usually loss of the 13q14 chromosomal region. Arguments could therefore be made for co-classifying these lesions, yet it seems to me more logical, given their clinicopathologic differences, to regard them as closely related but not identical. One can well imagine that a topic such as this may become controversial, especially since the same argument could be applied for DFSP and giant cell fibroblastoma.

2. Because fluorescence in situ hybridization (FISH) is easier to employ in paraffin-embedded tissue and is much less prone to false-positive results than RT-PCR, then FISH is becoming increasingly popular for the molecular diagnosis of soft tissue tumors. In this regard, one of the most widely applied tests is based on the use of split-apart probes around the \textit{EWSRI} gene. It has been recognized for some time that \textit{EWSRI} gene rearrangements are present in a variety of quite different tumor types – not only Ewing’s/PNET but also extraskeletal myxoid chondrosarcoma, clear cell sarcoma and desmoplastic small round cell tumor. However, more recent data have also shown that this gene is rearranged in so-called angiomatoid ‘MFH’ and personal experience indicates that it is also rearranged in a subset of myoepithelial tumors of soft tissue. While these data suggest that this gene is of enormous importance in mesenchymal tumorigenesis, it seems likely that more tumors showing this rearrangement will continue to be uncovered and this is likely to have practical daily impact both in terms of potential diagnostic confusion and also in selection of suitable technology for testing. Purely practical considerations suggest that it will be much more difficult for RT-PCR to become the test of choice on a broad scale in hospitals of all sizes.

3. Examples of fusion genes shared by quite different tumor types are increasingly recognized, making clear that morphologic correlation will almost always be an absolute necessity, rather than pathologists being able to rely purely on a molecular genetic diagnosis. An extreme example in this regard is the \textit{ETV6-NTRK3} fusion gene which,
when expressed in different cell lineages, appears to be the primary transforming event in infantile fibrosarcoma, congenital mesoblastic nephroma, secretory carcinoma of breast and in rare examples of acute myelogenous leukemia. Perhaps a better-known example is the substantial overlap between the ALK-related fusion genes in both inflammatory myofibroblastic tumor and anaplastic large cell lymphoma. However, potentially more confusing examples of such overlap are now being identified even within quite different tumors of mesenchymal type – the best example thus far is the recent demonstration of an identical EWSR1-CREB1 fusion gene in clear cell sarcoma arising at visceral locations as well as in so-called angiomatoid ‘MFH’. Fascinatingly, a minority of cases of so-called angiomatoid ‘MFH’ appear to show an EWSR1-ATF1 gene fusion, identical to that seen in clear cell sarcomas arising at somatic locations. This type of overlap, while being of considerable biologic and pathogenetic interest, is quite likely to give rise to confusion among non-specialists dealing with soft tissue sarcomas.

CONCLUSION

Evolution and advances in classification as well as our understanding of soft tissue tumors has been substantial in recent years and there is every sign that this will continue. Such advances will hopefully lead to an ever more logical and reproducible approach to both diagnostic and nosologic classification of these lesions, but there is still very much work to be done in trying to understand the basic biology of certain quite common tumor types and in the meaningful incorporation of molecular genetic data into any new classification scheme. For sure, this continues to be an exciting time to be interested in this field of pathology.