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UNDIFFERENTIATED SARCOMAS:
WHAT TO DO ? AND DOES IT MATTER ?
A SURGICAL PATHOLOGY PERSPECTIVE

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Bullet points

- Whether or not to label a sarcoma ‘undifferentiated’ depends heavily on available diagnostic resources and available treatment options.
- Pathologic subclassification of all sarcomas, where possible, is the main avenue by which advances in diagnosis, prognostication and therapeutic stratification are made.
- Attempts to subclassify round cell sarcomas are likely to have the highest yield, particularly in terms of clinical benefit.
- Subclassification of seemingly undifferentiated spindle cell sarcomas may sometimes have significant clinical impact.
- Efforts to subclassify undifferentiated pleomorphic or epithelioid malignancies arising in soft tissue is very often unrewarding.
**Introduction**

In the context of the program laid out for this session, which includes presentations devoted to the ultrastructure, cytogenetics and molecular genetics of poorly differentiated or undifferentiated sarcomas, then it is the purpose of this presentation to address specifically what surgical pathologists might do, in the routine clinical/diagnostic setting, to facilitate the classification of an otherwise seemingly undifferentiated sarcoma. Comprehensive lists of useful immunostains and specific cytogenetic/molecular genetic aberrations are not included here as they have been featured in many textbooks and review articles. In most institutions, it is the surgical pathologist who decides whether or not immunohistochemical stains, electron microscopy, cytogenetics or molecular genetic analysis should be initiated and, in these circumstances, it is important to consider what the cost-benefit of such testing might be and what impact any work-up (by whatever technique) may have either on prognostication or therapeutic decision making.

**What is an undifferentiated sarcoma?**

Either obvious or ridiculous as this may seem, the decision to label any sarcoma as undifferentiated is very much in the eye of the beholder. Furthermore, that beholder’s interpretation may be significantly influenced by the availability of resources to pursue the precise line of differentiation in a given neoplasm, as well as the likely influence of any more specific diagnosis on local treatment decisions. Factors which may have significant impact on whether or not to label a sarcoma as undifferentiated include:

- Clinical context/patient age
- Extent of tissue sampling
- Availability of immunohistochemistry (and range of antibodies)
- Availability of electron microscopy (including suitably fixed tissue)
- Availability of cytogenetic and molecular genetic testing
- Experience of the pathologist
- Availability of sophisticated oncologic intervention (including range of different therapies)
While, in academic ivory towers, we routinely take for granted the ability to apply a wide range of diagnostic techniques and the oncologists' ability to use a variety of different treatment modalities and chemotherapeutic regimens, on a broader scale, the range of diagnostic techniques or therapeutic approaches may be significantly more limited – or there may be a mismatch between the two. Very often, any limitations or mismatches will relate principally to issues of cost and/or proven cost-effectiveness. In general, however, it is probably not the pathologists' role to determine whether or not a tumor is worth subclassifying since, in many instances, the pathologist may not be familiar with the details of a specific clinical situation or with the possible and appropriate therapeutic interventions. Thus, the approach to cases of this type needs to be multidisciplinary and, as with all good pathology practice, should include effective communication between pathologists and clinicians. The extent to which a clinician is likely to seek detailed subclassification of a seemingly undifferentiated sarcoma will depend not only on the range of therapeutic options but on issues such as tumor stage, the patient's general clinical condition and an assessment of the likelihood that subclassification may have therapeutic impact (for example, this would be more likely in a round cell sarcoma rather than a pleomorphic sarcoma). Quite often, the more significant decision point, from the clinician's perspective, will be to make sure that the tumor is a sarcoma, rather than lymphoma, carcinoma or melanoma.

In general, undifferentiated sarcomas can best be considered in broad groups – principally those with round cell morphology, spindle cell morphology, pleomorphic morphology or epithelioid morphology. The proportion of undifferentiated sarcomas which would be labelled as myxoid is relatively small and, furthermore, most such lesions are of spindle cell type and occur in older adults, in a setting where therapeutic options are frequently more limited.

**ROUND CELL SARCOMAS**

Arguably, the subclassification of round cell sarcomas, most but not all of which occur in pediatric and adolescent patients, has the greatest clinical impact. The principal reasons for this are that these are among the most aggressive soft tissue sarcomas, yet also the most chemosensitive and, furthermore, there are well-defined
and quite different therapeutic regimens which are applied to rhabdomyosarcoma and Ewing’s sarcoma/PNET respectively, these being the two largest groups of round cell sarcomas. As such, pathologic subclassification will have significant impact on treatment and therefore best efforts have to be made to avoid the non-discriminatory label ‘undifferentiated’. That having been said, it is also true that a significant subset of the round cell sarcomas occurring principally in young infants may be extremely hard to classify reproducibly, either because they appear to be undifferentiated by whatever techniques are applied, or because they show bizarre or complex polyphenotypic differentiation or, more rarely, because there are well-documented examples in which the morphology and immunophenotype may not fit well with the genetic findings. In general, immunohistochemistry allows reliable subclassification of the large majority of round cell sarcomas occurring in young patients and, in the small subset which remain unclassified by this technique, most can be further resolved by using cytogenetics or, increasingly, molecular genetic analysis on paraffin-embedded or frozen tissue. While, in the past, electron microscopy was often quite helpful in this context, molecular testing has increasingly become the gold standard in this clinical setting, in part because of reproducibility and also in part because ultrastructural evidence of specific cytodifferentiation may be focal or limited in extent in a given tumor. In addition, tissues suitably fixed for electron microscopy are commonly not available. Furthermore, molecular genetic testing can be extremely helpful when there is immunophenotypic overlap between potential diagnoses – for example, keratin-positive Ewing’s/PNET, desmin-positive desmoplastic small round cell tumor and CD99-positive mesenchymal chondrosarcoma to name just a few.

Subclassification of round cell sarcomas in adult patients (of any age) also has direct relevance, now that pediatric-type rhabdomyosarcomas and Ewing’s/PNET are increasingly recognized in this age group. Subclassification is important because it is nowadays believed, principally by medical oncologists, that the use of pediatric-type chemotherapeutic regimens in adult patients with these diseases is associated with a significantly improved outcome.
SPINDLE CELL SARCOMAS

The true clinical relevance of subclassifying an otherwise seemingly undifferentiated spindle cell sarcoma is more limited than that in round cell sarcomas, mainly because of the more limited therapeutic options and smaller likelihood of chemo-responsiveness. While there is a good argument to make that pathologic subclassification of all sarcomas is worthwhile, since this is the only means by which clinical, prognostic and therapeutic differences will be identified, nevertheless, in the course of daily practice, the only two types of strictly spindle-celled sarcoma in which there may be important therapeutic implications are monophasic synovial sarcoma, which is especially chemo-sensitive (particularly to ifosfamide) and the fibrosarcomatous (higher-grade) variant of dermatofibrosarcoma protuberans (DFSP), which may be very usefully palliated (either in the setting of extensive local disease or metastatic disease) by the use of tyrosine kinase inhibitors such as Gleevec.

Conversely, the broader group of spindle cell sarcomas which might include mainly leiomyosarcoma, malignant peripheral nerve sheath tumor (MPNST) and, potentially, fibrosarcoma (if we could define it !) will have less importance at the present time, since this group of lesions as a whole is relatively less sensitive to currently available chemotherapeutic agents and, when either very large or else disseminated, is generally treated by one of the standard ‘broad spectrum’ adult-type sarcoma regimens (usually including either adriamycin and/or ifosfamide).

In terms of the techniques to apply, most examples of leiomyosarcoma and synovial sarcoma will be identified successfully using immunohistochemistry but, in poorly differentiated examples of synovial sarcoma, molecular genetic testing is often helpful. With regard to MPNST, greater problems arise since less than 50% of these lesions stain with either S-100 protein or GFAP and there are no well-defined molecular genetic ‘markers’ for this tumor type. In this setting, electron microscopy may well be useful in proving the presence of nerve sheath differentiation although, as mentioned above, the therapeutic impact of such classification may be more limited.
PLEOMORPHIC SARCOMAS

The subclassification of pleomorphic sarcomas which, following at least initial morphologic and immunohistochemical evaluation, appear to be undifferentiated is often frustrating and unrewarding. Among this group of sarcomas, evidence of a specific line of differentiation may be quite focal either by light microscopy (e.g. lipoblasts or osteoid) or, especially so, by electron microscopy. Thus, in this context, if immunostains fail to provide good evidence of a specific line of differentiation, electron microscopy is only rarely of help. Furthermore, this group of soft tissue sarcomas, with the sole exception of dedifferentiated liposarcoma (which retains the ring and giant marker chromosomes derived from the long arm of chromosome 12, as seen in well-differentiated liposarcoma), have non-specific complex karyotypes with no reproducible or diagnostically helpful aberrations. Similarly, these tumors generally lack any evidence of specific translocations that might be identified using FISH or RT-PCR. Importantly, however, as many as 95% of pleomorphic sarcomas can be subclassified using conventional immunostains, supplemented by EM where appropriate and it is nowadays recognized that such subclassification has clinical and prognostic relevance, since tumors showing any type of myogenic differentiation are associated with a much more aggressive clinical course. Thus, it is not good practice (and not good for patient care) to simply rename lesions formerly known as so-called ‘MFH’ as undifferentiated pleomorphic sarcoma, without first making reasonable efforts to subclassify the lesion by conventional means. The subset of pleomorphic sarcomas which do truly remain unclassifiable or undifferentiated generally seem to have an intermediate prognosis (with a 5-year metastatic rate in the range of 50%) and, when clinically indicated, these lesions, as with spindle cell sarcomas, are most often treated with one of the ‘broad spectrum’ adult-type sarcoma chemotherapeutic regimens.

SARCOMAS WITH EPITHELIOID MORPHOLOGY

Most well-defined forms of sarcoma with epithelioid morphology (principally epithelioid sarcoma, epithelioid angiosarcoma, epithelioid GIST, epithelioid MPNST, etc.) can readily be recognized and reproducibly diagnosed based on clinical context, morphology and immunostains. However, at least in my experience, there exists a significant subset of poorly differentiated epithelioid malignant neoplasms, presenting in
soft tissue with no apparent evidence of a primary neoplasm elsewhere, in which the
differential diagnosis lies between an undifferentiated sarcoma with epithelioid
morphology, metastatic carcinoma or metastatic melanoma. Very commonly, extensive
immunostains fail to reveal any evidence of epithelial or melanocytic differentiation and,
in the setting of clinical evidence that the soft tissue mass is the primary lesion, then
there is little option but to regard these as some type of undifferentiated sarcoma.
Tumors in this general category have not been well documented or extensively
described in either the pathologic or clinical literature and there are virtually no data as
to the behavior and treatment response of such neoplasms. In general, it seems that
these lesions can only be labelled as sarcoma as a diagnosis of exclusion, since there
are no markers which specifically recognize mesenchymal differentiation. Having said
that, if all epithelial markers are negative and there is readily identified CD34 positivity,
then this generally would argue quite strongly against a diagnosis of carcinoma. When
dealing with tumors in this category, at the present time, it seems that pathologists can
do little more than to exclude the possibility of a metastatic epithelial/melanocytic
neoplasm (or perhaps anaplastic large cell lymphoma), but further attempts to identify a
specific line of differentiation thereafter are almost always fruitless. Lesions of this type
warrant further more detailed pathologic study, particularly since this may assist in
better definition of the optimal therapeutic approach to such enigmatic neoplasms.

CONCLUSION

In general terms, careful sampling combined with immunohistochemistry and
molecular genetic testing, where appropriate, allows meaningful classification of many
of the lesions initially thought to be undifferentiated. In my personal experience, it
seems that the role of electron microscopy is becoming increasingly limited, although in
part this also reflects diminished availability of this element of technical infrastructure.
In general, subclassification of undifferentiated round cell sarcomas, where possible,
has the greatest clinical impact and the subclassification of seemingly undifferentiated
spindle cell sarcomas, if feasible, is also sometimes useful. At this point in time, so long
as reasonable efforts are made to subclassify any pleomorphic or epithelioid
malignancy arising in soft tissue by conventional light microscopic means, then further
attempts to subclassify the subset of these lesions which appear to be truly
undifferentiated are, unfortunately, often unhelpful and the clinically beneficial yield is low.