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Short Course 8

Recent advances and controversies in soft tissue pathology

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This course on soft tissue tumor pathology has been designed with the aim to highlight some important problematic and controversial issues of clinical, diagnostic and conceptual significance. The role of the soft tissue tumor pathologist is constantly changing. Despite the increasing demands and difficulties involved in this area, soft tissue tumor pathology continues to be an irresistible challenge to many pathologists. The pathologist is not only expected to stay abreast of the ever-growing number of new soft tissue entities and their variants/subtypes, to be aware of the rapidly increasing number of ancillary diagnostic techniques, to know how to correlate tumor genetics and molecular biology with the daily practice of surgical pathology and to keep up with the constantly changing treatment protocols and their effects on tumors. He or she is also expected to be a central figure in the multidisciplinary soft tissue tumor team.

The basic problems involved in soft tissue tumor typing and their prognostication will be discussed by Dr. A. Nascimento of the Mayo Clinic, where tumor grading was born, as well as by Dr. J.M. Meis-Kindblom from Sahigren Hospital and the Musculoskeletal Tumor Center in G6teburg, Sweden.

Dr. W. Ryd, chief of cytopathology at Sahlgren Hospital, will report his vast experience with fine needle aspiration (FNA) cytology in the preoperative diagnosis of soft tissue tumors. It is apparent that soft tissue tumor FNA poses special diagnostic problems. However, when the FNA findings are interpreted by someone with a deep knowledge of the area and in the context of a multidisciplinary approach to treatment, it is clear that FNA provides safe, fast and accurate diagnoses comparable to those obtained with coarse needle biopsies and even open surgical biopsies. Although the longest experience with ENA has been in Sweden, there is an increasing worldwide interest in the area. Dr. A. Nascimento will report the more recent experience of the Mayo Clinic with FNA.

Immunohistochemical techniques applied in the studies of soft tissue tumors have proved to be useful with regard to tumor classification as well as more basic questions regarding origin and differentiation, biological behavior, prognosis and treatment. Dr. M. Miettinen, chief of the Soft Tissue Branch at the AFIP, will give us his personal views regarding the role of immunohistochemistry in the diagnosis of soft tissue tumors and an update on new markers in this field.

Dr. J.M. Lopes of Porto, Portugal will discuss topics of general interest related to synovial sarcoma, one of the more common adult soft tissue sarcomas. Recent studies indicate that patients with synovial sarcoma (which has traditionally been viewed as a uniformly high-grade sarcoma) can be divided into favorable and unfavorable groups based on certain clinical and morphological factors in addition to certain biological markers.

With the exception of hematological-lymphoreticular neoplasms, there is hardly any other area in which tumor cytogenetics and molecular biology have been so fruitful as in the area of soft tissue tumors. Numerous tumor-specific genetic changes have been identified that are diagnostically useful. They have also helped us to understand some of the genetic-molecular biological basis of neoplastic transformation and progression. Despite these impressive advances, a traditional pathologist could argue that most of these new findings have only proven that the conclusions drawn by experienced and gifted morphologists were indeed correct. Dr. V.P. Collins of Cambridge, England, is one of those rare pathologists who embodies the traditional pathologist in the best sense and the new molecular pathologist. He will explain what the new molecular techniques can offer today and what we can expect in the future.

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Grading of sarcomas at the Mayo Clinic 75 years after Broder

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The process of grading cancer was born at the Mayo Clinic about 80 years ago with Dr. Albert Compton Broders. Broders joined the Mayo Clinic in 1912 and later in 1920, as a consultant in surgical pathology and an instructor of pathology, he published the seminal paper that introduced the important but controversial issue of histopathological grading of cancer.

In his initial paper, following the principle that under certain conditions of growth and environment, epithelial cells may lose all traces of their epithelial origin and may actually become indistinguishable from connective tissue elements, Broders (1) used the criteria of differentiation to grade 537 squamous cell carcinomas of the lip. According to Broders, differentiation is the phenomenon by which the product of a growth, cancerous or not, is similar to a normal epithelium and he used to give the example of the production of a "pearly body" in a squamous cell carcinoma as the ultimate step of differentiation.

According to Broders (1), squamous cell carcinomas should be graded according to their differentiation and mitotic activity and although he developed rules to grade the tumors using the criteria of differentiation, he never elaborated much on the issue of mitotic activity, limiting his comments to the observation that the higher the histopathological grade of a carcinoma, the more mitotically active the process. Broders divided the 537 squamous cell carcinomas of the lip into four grades. To do this, he used the following method: grade 1 /E over 3/4 differentiated epithelium and less than 1/4 undifferentiated elements; grade 2 /E differentiated epithelium undifferentiated epithelium; grade 3 /E over 3/4 undifferentiated epithelium and less than 1/4 differentiated epithelium and grade 4 /E 100% undifferentiated epithelium. According to this method, 15.82% of the tumorsweregrade 1;62.01%, grade2; 21.04%, grade3and 1.13%, grade 4. He found a death rate of zero, 54.90%, 84.21% and 100% for grades 1, 2, 3 and 4, respectively.

In a second paper in 1921 (2), Broders studied 256 squamous cell carcinomas of the skin, using the same grading method, and found a death rate of zero for grade 1, 61.29% for grade 2, 85.71% for grade 3 and 100% for grade 4 carcinomas. Later, Broders (3) slightly modified his grading scheme in the following way: grade 1 /E up to 25% of undifferentiated epithelium; grade 2 /E 25-50% of undifferentiated epithelium; grade 3 /E 50-75% of undifferentiated epithelium and grade 4 /E over 75% of undifferentiated epithelium. He also extended his work to include other carcinomas such as uterine and breast carcinomas (3).

Despite his enthusiasm for histopathological grading, Broders (3) recognized that other factors, such as size and gross morphology of the cancers, could play important roles in the behavior of these lesions. He used to exemplify this view with a citation by Dr. W.W. Mayo: "A cancer that comes to you is less malignant than one that goes away from you," meaning that papillary or polypoid carcinomas are usually less malignant than the flat or infiltrating ones.

Broders' work with carcinomas was extended to bone and soft tissue sarcomas by Dahlin and Soule, respectively, at the Mayo Clinic. According to Dahlin and later to his most notable disciple K.K. Unni (4), most bone sarcomas may be graded using Broders' principles. The criteria of differentiation used by Broders for carcinomas is translated in sarcomas by degree of anaplasia of the cells that are mainly judged by the degree of nuclear atypia and pleomorphism. According to Unni and Dahlin (4), two important points should be taken into consideration when one is grading bone sarcomas: i) only tumors that show histological variation can be graded; and ii) most bone tumors show uniformity in their differentiation throughout their substance. This means that it is unlikely that a grade 1 sarcoma will show grade 4 areas, and when this happens, we should assume that a phenomenon of "dedifferentiation" has occurred.

In following these principles, we accept that some bone tumors such as Ewing's sarcoma, myeloma, chordoma, adamantinoma and mesenchymal chondrosarcoma should not be graded and histopathological grading is an important feature in the determination of prognosis for sarcomas such as osteosarcomas, chondrosarcomas, fibrosarcomas and angiosarcomas (4). The late Dr. Edward H. Soule, a prominent surgical and soft tissue pathologist at the Mayo Clinic, followed the same principles in grading soft tissue sarcomas (5).

No other variable seems to work better in the prediction of the behavior of soft tissue sarcomas than histological grade, but at the same time, no other prognostic factor has been responsible for so much controversy and debate. Soft tissue sarcomas are a large group of different clinical entities that, despite sharing common clinical features such as blood-borne metastatic spread, also present significant clinical differences. The value of histopathological grading should, therefore, be balanced against the predictive significance of other histological and/or clinical parameters that vary according to the specific type of sarcoma.

Nowadays at the Mayo Clinic, soft tissue sarcomas are graded by taking into consideration mitotic activity, presence of necrosis, cellularity and cellular atypia and pleomorphism. Based on these characteristics, we divide soft tissue sarcomas in a four-grade system which can easily be transformed in a two-grade system with Mayo's grade 1 and 2 corresponding to low grade sarcomas and grades 3 and 4 to high grade sarcomas. We recognize there is a tendency to overuse the intermediate grade or grades when using three or four-grade systems with consequent impairment of the predictive value of grading.

Points to remember when one uses mitotic activity to grade soft tissue sarcomas include: i) the fact that delay in the fixation of the specimens can cause an artifactually low mitotic count (6); ii) the fact that mitotic count should never be used as a single criterion to determine malignancy in a spindle cell lesion or to grade a sarcoma; and iii) the quality of the mitotic figures is as important as the quantity of mitoses in determining the malignant nature of a process as well as the grading of a soft tissue sarcoma.

Care should be exercised when using necrosis to grade soft tissue sarcomas. Necrosis should be evaluated in areas of the tumor away from zones of epidermal or mucosal ulceration. One should also be aware of previous surgical procedures such as fine needle aspiration biopsy to avoid evaluating necrosis in such areas. It should be remembered when evaluating consultation cases that the presence of necrosis can be biased by the fact that pathologists in general have a tendency to skip necrotic areas when performing the gross examination of tumors. Also, we should remember that benign lesions, such as benign cutaneous fibrous histiocytoma and myofibromatosis, can display necrosis.

The cellularity of a sarcoma is usually inversely proportional to the amount of intercellular matrix and richly collagenized sarcomas (such as some examples of fibrosarcomas) and richly myxoid neoplasms (such as some myxofibrosarcomas) have a tendency to behave in a low-grade fashion.

When judging cellular anaplasia and pleomorphism, one should be careful to interpret degenerative atypia, such as that observed in schwannomas, neurofibromas and lelomyomas, as evidence of malignancy.

At the Mayo Clinic, we find it important to grade histologically most of the spindle cell sarcomas, such as adult fibrosarcomas, myxofibrosarcomas, lelomyosarcomas, malignant peripheral nerve sheath tumors and the debatable hemangiopericytomas. We do not grade infantile fibrosarcomas, atypical fibroxanthomas, noncomplicated dermatofibrosarcoma protuberans, plexiform fibrohistiocytic tumors, angiomatoid malignant fibrous histiocytomas and epithelloid hemangloendotheliomas because they are by definition low grade. Likewise, we do not grade pleomorphic and giant cell variants of malignant fibrous histiocytomas, rhabdomyosarcomas, Ewing's sarcoma and primitive neurooectodermal tumors, mesenchymal chondrosarcoma, desmoplastic small round cell tumors, synovial sarcomas, mesotheliomas, clear cell sarcomas, extraskeletal osteosarcomas, alveolar soft part sarcomas and epithelloid sarcomas because these tumors, despite histopathological picture, display a uniform

high-grade behavior. Liposarcomas are graded according to subtype, with well-differentiated and myxoid liposarcomas being grade 1 and 2, respectively, while round cell, dedifferentiated and pleomorphic liposarcomas are, by definition, high-grade sarcomas. Angiosarcomas are graded according to differentiation, with highly vascular neoplasms representing the low-grade end of the spectrum and solid tumors considered as high grade. However, in soft tissues, angiosarcomas have a tendency to behave aggressively, no matter what their histology looks like.

Finally, it should be emphasized that in grading of soft tissue sarcomas, sampling is the greatest pitfall. Benign neurofibromas and grade 4 malignant peripheral nerve sheath tumors can share space in the same tumor and retroperitoneal liposarcomas can display areas of dedifferentiation side by side with grade 1 well-differentiated liposarcoma. This phenomenon casts some doubts in the usefulness of fine needle aspiration biopsies in the grading process of soft tissue sarcomas.

References

1. Broders AC. *Squamous cell epithelioma of the lip. A study of five hundred and thirty-seven cases.* J Am *Med* Assoc 1920; 74: 656-664.
2. Broders AC. *Squamous cell epithelioma of the skin. A study of256 cases.* Ann Surg 1921; 73: 141-160.
3. Broders AC. *The microscopic grading of cancer* In: Pack GT, Livingston EM. (Eds.). Treatment of *Cancer* and Allied Diseases. Paul B. Hoeber, Inc., New York 1946; 2:19-41.
4. unni KK, Dahlin DC. *Grading ofbone tumors. Sew* Diagn Pathol 1984; 1:165-172.
5. Pritchard DJ, Soule EH, Taylor WE at al. *Fibrosarcoma-a clinicopathologic and statistical study of 199 tumors of the soft tissues of the extremities and trunk.* Cancer 1974; 33: 888-897.
6. Jensen aM, Hogh J, Ost§aard SE at al. *Histopathotogical grading ot soft tissue tumors. Prognostic significance in a prospective study of 278 consecutive cases.* J Pathol 1991; 163: 19-24.

On the comparison of apples, oranges and sundry fruits: Problems with grading and prognostication in soft tissue tumors

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Grading of tumors began in the early part of this century with Broder, who used a four-tiered grading scheme for carcinomas and eventually for sarcomas. Since then, various types of grading schemes have been used – some of these continue to use four grades (as we do in Goteborg) while others use three and others use two. Grades III-IV in the four-tiered system and grades II-III in the three-tiered system correspond roughly to high-grade tumors.

In most sarcoma grading schemes, the degree of histological differentiation, cellularity, pleomorphism, mitotic activity, necrosis and vascular invasion are taken into account. In addition, some grading schemes take the pathological diagnosis into consideration, recognizing that certain sarcomas have a specific biological behavior *(i.e.,* the grade is inherent in the diagnosis). Most grading schemes separate low-grade from high-grade tumors, allowing treatment decisions to be made. However, they have not been completely satisfactory in terms of predicting prognosis. Therefore, attempts to refine grading schemes have been made: i) using flow cytometry to separate diploid from aneuploid tumors and to identify the S-phase fraction; ii) using markers such as Ki67 (MIB 1) to more accurately assess proliferative activity; and iii) looking for p53 expression, MDM2 expression and RB gene product expression among others to identify potentially more aggressive sarcomas.

There are several underlying assumptions in most grading schemes. Some of these assumptions are not valid, in our opinion, and account, in part, for the failure of most grading schemes to consistently function well. There are over 250 soft tissue diagnoses; approximately 50 of these represent sarcomas. The same histological grading criteria have been applied to 50 different types of sarcoma, despite the fact that some behave as borderline or low-grade malignant tumors (e.g., dermatofibrosarcoma protuberans) and others are uniformly high grade.

Another problem with grading is that the concept of low and high grade is ambiguous and simplistic from a biological perspective. What is meant by a low-grade tumor? Does it mean only a long survival despite repeated local recurrences, a long disease-free survival or a long survival despite the presence of metastasis with an ultimate tumor-related death (as in some cases of extraskeletal myxoid chondrosarcoma)? The problems in defining a high-grade tumor are even more complex. Does a high-grade tumor mean only that survival is short or that the tumor metastasizes early, whether or not it leads to the patient's demise? Does it include locally aggressive, nonmetastasizing tumors that frequently cause an early death?

Another problem with grading schemes is the accurate assessment of necrosis. Ideally, this should be done macroscopically and verified with histological sections, since all areas that may appear to be necrotic to the naked eye may not be so. The extent of necrosis may be prognostically significant in some sarcomas but not in others *(i.e.,* in some sarcomas, the presence of any necrosis, even if only microscopic, may be a bad prognostic feature). Moreover, necrosis is often an intrinsic part of some tumors (as in epithelloid sarcoma). It may be influenced by location where tumor expansion is limited, such as in the finger or foot and the prognostic significance of necrosis in such cases is questionable. Similar arguments can be made with regard to differentiation, cellularity, pleomorphism, mitotic activity and vascular invasion with specific sarcomas.

Most sarcomas are graded as high grade in current grading schemes regardless of which system is used. Since the overwhelming majority of adult soft tissue sarcomas are liposarcoma and so-called malignant fibrous histiocytoma, the current grading schemes have (by default) functioned reasonably well. However, the discriminating ability of current grading schemes is significantly less for rarer tumors. We have found that specific sarcomas, such as synovial sarcoma, extraskeletal myxoid chondrosarcoma, clear cell sarcoma, angiosarcoma of deep soft tissue, malignant granular cell tumor, intravascular lelomyosarcoma and malignant peripheral nerve sheath tumor have specific prognostic criteria. In some of these entities (e.g., intravascular lelomyosarcoma, malignant granular cell tumor and deep soft tissue angiosarcoma, which are nearly always uniformly high-grade lesions), the diagnosis dictates the tumor grade and predicts clinical behavior. In others, such as synovial sarcoma, histological grading using specific criteria is the single most important prognosticator, whereas in extraskeletal myxoid chondrosarcoma, the clinical features of age and tumor size are