Everything is spindle - how far can we go with limited FNA material?

Paul E. Wakely, Jr., M.D.
The Ohio State University Wexner Medical Center
Columbus, OH

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Fine needle aspiration (FNA) biopsy as applied to the diagnosis of soft tissue (ST) masses is extremely demanding, difficult and controversial. Its use on a regular basis in the U.S./Canada is confined to a small number of medical centers because of the limitations imposed by the nature of the technique, and by the infrequency, unfamiliarity, heterogeneity, and overlapping features of ST neoplasms. Compounding this difficulty is an absence of spatial relationships in FNA in contrast to those appreciated in tissue sections, an inability to produce “mitotic counts” or extent of necrosis, and the chronic battle to procure a sufficient number of cells for evaluation. In this ASC evening session, I have been asked to discuss spindle cell lesions.

Even though this is a broad topic, when most pathologists use the phrase “spindle cell lesion/neoplasm” they summon a mental image of a population of more or less monotonous cells with elongated nuclei lacking significant pleomorphism, e.g. the ‘fibrosarcoma phenotype’ of bygone days. Thus, I will attempt to limit this discussion regarding the diagnostic performance of FNA to a limited number of spindle cell lesions that mimic this morphologically monotonous cell proliferation in the presence of a ‘clean’ smear background. By doing so, this excludes a large number of spindle cell lesions commonly associated with other features on the smear such as myxoid/chondromyxoid change, calcification, and the presence of other cell types (inflammatory cells, giant cells, adipocytes, pleomorphic or epithelioid cells). Benign entities discussed include fibromatosis, benign nerve sheath tumors, and sundry benign spindle cell proliferations. Malignant neoplasms conforming into this restricted definition include synovial sarcoma, GIST, MPNST, and less common miscellaneous sarcomas (w-d leiomyosarcoma, DFSP, and low-grade fibromyxoid sarcoma).

Fibromatosis

The several clinicopathologic subtypes of fibromatosis yield similar cytopathology. Smears show a range of cellularity but are typically hypocellular with a clean background. Isolated or loose clusters of spindle and stellate cells are seen with collagenous stroma. Oval to elongated smoothly contoured nuclei possess small nucleoli, finely dispersed chromatin, and thin delicate, wispy unipolar and bipolar cytoplasmic tendrils. The amount of collagenous stroma is usually scant. Atrophic myofibers with clustered nuclei may mimic multinucleated giant cells. A large study of 69 patients with histologically proven desmoid tumors showed an accuracy of 94% in differentiating a benign from malignant process, and 51% specifically recognized as desmoid fibromatosis. Review of our own unpublished cases (n= 17; 2005-2015) showed ‘benign vs. malignant’ accuracy = 100%, specific diagnosis = 47%, and combined
‘fibromatosis/suspicious for fibromatosis’ diagnosis = 76%. All cases but one were primary lesions; only two cases had β-catenin staining performed.


**Benign Nerve Sheath Tumor [BNST]**

Distinction between schwannoma and neurofibroma is difficult; some feel these should be grouped together as BNST. Resnick Neurofibromas are typically much less cellular than schwannoma. Insufficient cell number and other features such as cystic change or hyalinization, or severe pain during the FNA prematurely ending the procedure are reasons for non-diagnostic aspirates. Domanski BNSTs have spindle cells in syncytial clusters & scattered single forms, the latter often with stripped bare nuclei. Parallel and random arrangements of nuclei with palisading can be seen. Verocay bodies are distinctly unusual. Domanski Cells have pale ill-defined cell borders and wispy or ropy cytoplasmic processes. Spindle shaped nuclei may have smooth or irregular contours described as buckled, wavy. Klijianenko Isolated nuclear enlargement, pleomorphism, and intra-nuclear inclusions are more typical of “ancient” change in schwannoma. Smear background typically lacks vascularity, necrosis, and mitotic figures Chebib et al. found that when 5 features [high numbers of clusters, few to no single cells, fibrillary stroma; 'pointy' nuclear tips; and anisonucleosis] were present, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for diagnosing schwannoma were 22%, 97%, 81%, and 68%, respectively. Review of our cases from the past decade (n=31) uncovered 26 schwannomas and 5 neurofibromas. None were diagnosed as malignant, but 2 were called ‘suspicious for sarcoma’. A specific FNA diagnosis of schwannoma was made in 85% of 26 cases, and benign nerve sheath tumor in 60% of 5 neurofibromas.

Cellular schwannoma however is a major pitfall because of highly cellular microfragments combined with nuclear pleomorphism. Henke Useful immunohistochemistry (IHC) includes intense S-100 and SOX10 staining in the cell-block.

Miscellaneous Benign

The cytopathology of solitary fibrous tumor (SFT) is not sufficiently distinctive to allow a specific diagnosis without the use of IHC. Smear cellularity varies from low to highly cellular with a clean or bloody background. Banal appearing cells in a dissociated pattern have isomorphic spindle and oval-shaped nuclei with thin cytoplasmic strips interspersed with stripped nuclei. Anisonucleosis is minimal, and nuclear chromatin is evenly dispersed, finely granular, and lacks enlarged nucleoli. Irregular ropy collagen fibers may contain embedded spindle cells. Unlike large tissue specimens, cytopathology is unable to recognize hyper- and hypocellular zones or a hemangiopericytomatic vascular pattern. Review of our own cases (n=8) from the past decade shows a wide range of diagnoses as none of them had confirmatory IHC. Malignancy is difficult to recognize in SFT aspirates. Some reports show no difference in cellularity between benign and malignant examples. Others however describe an increased cellularity, individual cell necrosis, and round or epithelioid forms, yet individual cytomorphology remains similar with minimal nuclear pleomorphism.

Leiomyoma of somatic soft tissue is uncommon. Most reports are from visceral organs, and some of these earlier reports may be examples of gastrointestinal stromal tumor (GIST) in retrospect. Microfragments contain banal appearing spindle cell nuclei insinuated in an abundant fibrillar cytoplasmic syncytium with few dissociated single cells. Syncytial clusters show nuclei in regular parallel alignment with little nuclear overlap. These aggregates do not display the high cellularity associated with other spindle cell sarcomas. Nuclei are oval to elongate with minimal waviness, fine chromatin, and faint nucleoli. There is an absence of multinucleated cells, vascularity, and necrosis. In the GI tract, the principal diagnostic differential is with GIST. These two neoplasms have such overlapping cytomorphology that IHC is necessary. Of the 6 histologically confirmed leiomyomas in our files (all primary esophageal masses), a specific diagnosis was made in 67%, a ‘suspicious for leiomyoma’ in 17%, and ‘spindle cell neoplasm’ in 16%.


Gastrointestinal Stromal Tumor (GIST)

A specific diagnosis of GIST is readily attainable nowadays when one employs a cell block along with smears that demonstrates the relatively specific DOG-1+/CD117+ combination. Smears are usually highly cellular, single and in syncytial clusters, and displaying monotonous spindle-shaped nuclei with epithelioid cells seen in a minority of
cases. With the exception of minimal to no nuclear atypia in GIST, the cytomorphology between it and schwannoma or leiomyoma overlap considerably. Major prognostic parameters for GIST such as tumor size and mitotic index are unavailable with cytologic specimens. Review of our surgically confirmed cases from the past decade (n=41, 39 primary tumors) reveals an accuracy of 98% in correctly diagnosing GIST from the FNA material alone. The single case diagnosed as ‘favor GIST’ had no IHC.


Synovial Sarcoma

Most spindle cell sarcomas require accompanying ancillary IHC, or cytogenetic analysis for a specific diagnosis. Synovial sarcoma (SS) serves as a paradigm for spindle cell malignancies characterized by cell monotony. FNA smears contain a rich cell yield dispersed as single cells and in thick, 3-D clusters having multiple cell layers. Relatively uniform rounded to spindle shaped intermediate-sized cells with oval to oblong monotonomous nuclei, evenly dispersed chromatin, inconspicuous to absent nucleoli, and smooth contours combine with scant non-vacuolated cytoplasm. There is minimal background stroma. The biphasic variant of SS (gland formation) is difficult to appreciate on smears.

Differential diagnosis includes MPNST, cellular solitary fibrous tumor, low-grade leiomyosarcoma. With the advent of PCR and FISH testing for the t(X;18) translocation, a specific diagnosis of SS is now possible using FNA cytology without resorting to tissue biopsy. Srinivasan, Åkerman Review of our last 16 cases (unpublished data) shows an accuracy of 81% in making a specific diagnosis of SS by FNA using smears; when coupled with testing for t(X;18) using a commercially available FISH probe (n=13) the accuracy was 100%. Srinivasan showed similar results in 6 cases with RT-PCR testing.

- Åkerman M, Ryd W, Skytting B. Fine-needle aspiration of synovial sarcoma: criteria for diagnosis: retrospective reexamination of 37 cases, including ancillary diagnostics. A
Malignant Peripheral Nerve Sheath Tumor [MPNST]

The principal cytologic feature of MPNST is marked spindle cell hypercellularity arranged in both aggregates and as single forms. Spindle cells show variable anisonucleosis of serpentine, rounded, and oval nuclei depending on tumor differentiation. Well-differentiated MPNST aspirates show similar-sized nuclei with overlapping and slight to moderate contour irregularity, but not the accentuated serpiginous shapes seen in most examples of neurofibroma. This undulating nuclear quality is replaced in poorly-differentiated examples with nucleomegaly, multinucleation, and obvious pleomorphism. N/C ratio is high and cell cytoplasm is non-vacuolated. Nucleoli are indistinct in well-differentiated examples, but visible in anaplastic examples. Poorly-differentiated examples also show mitotic figures, individual cell necrosis, and the cytopathologic features described for undifferentiated pleomorphic sarcoma.

MPNST closely mimics monophasic synovial sarcoma and other spindle sarcomas. Without IHC a specific diagnosis is reached in <50% of cases. Knowledge that the neoplasm has arisen from a nerve or in a patient with NF-1 are the most useful pieces of information to allow for a specific diagnosis. This was demonstrated in our own large series of 55 cases where a definitive diagnosis of either MPNST or consistent with MPNST was issued in 30%, 93%, and 70% of primary, locally recurrent, and metastatic lesions respectively.


Miscellaneous Spindle Cell Malignancies

Localization of dermatofibrosarcoma protuberans (DFSP) primarily to the dermis and subcutis of the trunk and proximal extremities is a major factor in its recognition when a highly cellular aspirate dominated by spindle cells is found. Nonetheless, a specific diagnosis is difficult without IHC staining, or knowledge of a previous history of DFSP. Some claim to appreciate a storiform pattern in smears, but in this authors opinion this is highly subjective, and does not seem to be useful in recognizing this neoplasm. Hypercellular 3-dimensional aggregates are populated by fusiform cells showing minimal anisonucleosis. Cells have evenly dispersed chromatin in oval to elliptical nuclei, vague nucleoli, and modest amount of cytoplasm. Often, these are embedded within a small-moderate amount of metachromatic staining collagen. Also, smears typically contain numerous dissociated spindle cells having short cytoplasmic processes and bare nuclei.

Fibrosarcoma arising in DFSP is probably impossible to distinguish from DFSP and other spindle cell sarcomas using FNA-based cytologic preparations alone. In addition to spindle cell
sarcoma, the differential diagnosis includes solitary fibrous tumor, nodular fasciitis, spindle cell melanoma, perineurioma, and cellular benign fibrous histiocytoma.

Spindle cell melanoma can be extremely difficult to separate from spindle cell sarcoma. Knowledge of a prior history of melanoma is probably the most helpful information one can obtain to avoid diagnostic error. This variant often lacks cytoplasmic pigment; in one large series it was present in only 15% of cases. Piao Other features characteristic of the “cytomorphologic signature” of melanoma including eccentric (plasmacytoid) nuclear positioning, binucleation/multinucleation, macronucleolus, and intranuclear cytoplasmic inclusions are more evident in the epithelioid variant. Piao Spindle cell nuclei may display moderate-marked nuclear pleomorphism or appear cytologically bland and monotonous. A full complement of IHC markers (S-100, SOX10, HMB-45, Melan-A) may be necessary to recognize this variant of melanoma.


Aspirates of leiomyosarcoma (LMS) contain not only hypercellular microfragments, but the tightly cohesive cell syncytium of leiomyoma transforms to more loosely clustered cells, and isolated cells. Barbazza Tumor grade dictates cell size, shape, and uniformity. Spindle-shaped cells with minimal anisocytosis, long cytoplasmic processes, but increased cellularity exist in low-grade LMS smears. High-grade forms mimic smears of undifferentiated pleomorphic sarcoma. That is, dissociated cells become much larger, have moderate-marked nuclear pleomorphism (rounded, spindle, bizarre shapes), two or more nuclei per cells, coarse chromatin, macronucleoli, variable amounts of misshapen cytoplasm, and often lose any semblance of regular linear parallel organization. Klijianienko,Tao González-Cámpora Cellular necrosis and mitotic figures also more apt to be found in high grade LMS. The myxoid form of LMS is easily confused with myxofibrosarcoma, and IHC is required to recognize high-grade LMS as showing smooth muscle differentiation. Of 8 cases from our recent material, 50% were specifically diagnosed as LMS (all with confirmatory IHC), and 50% as spindle cell sarcoma/neoplasm (none having IHC).

Low grade fibromyxoid sarcoma (LGFS) must be considered in a hypocellular aspirate consisting of bland spindle cells and a myxoid background. The capillary network seen histologically is rarely demonstrable in aspiration smears. Most authors describe bland spindle cells in clusters and loose fascicles in a collagenous, myxoid matrix, but conclude that the cytologic findings are too non-specific to allow for a definitive diagnosis. If one thinks to perform cytogenetic or molecular analysis for t(7;16)(q34;p11) then a specific diagnosis may be possible.

The variant containing giant collagen rosettes has not been fully described in the cytology literature. Our unpublished experience shows hypocellular smears containing large rounded fragments of metachromatic staining fibrous tissue mimicking collagen rosettes containing cytologically banal spindle cells. Cells embedded within the collagenous matrix are difficult to visualize, but surrounding this matrix are oval, rounded, and fusiform nuclei with scant cytoplasm and many stripped nuclei in a clean background.

- Domanski HA et al. LGFMS is difficult to diagnose by FNA cytology: a cytomorphological study of 8 cases. Cytopathology 2009; 20:304-14.