

Soft Tissue Sarcomas

The Usefulness and Limitations of Fine-Needle Aspiration Biopsy

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The diagnosis of soft tissues sarcomas by fine-needle aspiration biopsy (FNAB) is controversial and relatively underused. We believe that the lack of acceptance by many clinicians and pathologists may be related to several factors. First, in comparison with other forms of cancer, soft tissue sarcomas are rare, constituting less than 1% of all malignant neoplasms.¹ As a consequence, most pathologists lack extensive experience with the histopathologic and cytopathologic features of sarcomas. Furthermore, possibly no other subspecialty field of pathology is associated with a more bewildering spectrum of histomorphologic appearances. Because a diagnosis of malignant neoplasm may result in adverse consequences (eg, amputation), the pathologist involved with a soft tissue tumor diagnosis, especially with small biopsy specimens such as FNAB specimens, may be reluctant to give a specific diagnosis. Finally, of the pathologists with experience in the diagnosis of soft tissue sarcoma, many have been reluctant to endorse FNAB as a reliable procedure for establishing a definitive diagnosis.² Nevertheless, FNAB among adequate specimens seems to have a diagnostic sensitivity and specificity of up to 95% for the determination of malignancy.^{3,4} False-positive and false-negative results approach approximately 4% (not including inadequate samples).⁴ If inadequate samples are included, false-negative rates may approach 10% to 15%.^{3,4} In this review, it is our intent to provide a comprehensive overview of the usefulness and limitations of FNAB in the diagnosis of soft tissue sarcomas, including a reappraisal of diagnostic criteria.

Clinical and Radiologic Correlation

Correlation with clinical and, when necessary, radiologic features is important for establishing a soft tissue tumor diagnosis. Plain film radiographs, computed tomography scans, and magnetic resonance imaging often help reveal the location (eg, cutaneous vs intramuscular), size, evidence of bone involvement (eg, primary bone tumor vs soft tissue tumor), homogeneity vs

heterogeneity, and relationships to neurovascular structures (eg, nerve sheath tumor). Such data when coupled with cytomorphologic findings may help to provide a “definitive” diagnosis, obviating the need for a second, more costly diagnostic procedure (eg, incisional biopsy). **Table 1** summarizes the clinical, radiologic, and pathologic features that assist in the differential diagnosis of benign vs malignant soft tissue tumors. In general, soft tissue sarcomas are large, deeply seated masses that on FNAB usually yield hypercellular smears composed of mostly discohesive hyperchromatic cells with obvious malignant nuclear features. However, the difficulty of interpreting some benign and low-grade malignant neoplasms is worthy of additional comment. By FNAB, desmoid tumors (fibromatoses) may be difficult to diagnose, as cytologic preparations may be sparsely cellular. Furthermore, “desmoidlike areas” within fibrosarcomas may be inadvertently sampled. Unlike most benign soft tissue tumors, aspirates of nodular fasciitis are frequently hypercellular containing mostly discohesive tumor cells. Nevertheless, clinically significant nuclear atypia is lacking. Clinically, in comparison with sarcomas, most examples of nodular fasciitis are more superficially located, exhibit very rapid growth, and are of relatively small size (eg, <2 cm).

Practical Approach to the Cytologic Diagnosis

For convenience, some authors have subdivided soft tissue sarcomas into various categories based predominantly on overall cytomorphologic features.⁵ These categories are summarized in **Table 2** and include such designations as small round cell sarcomas, spindle cell sarcomas, epithelioid/polygonal sarcomas, pleomorphic sarcomas, and myxoid sarcomas. Such classifications may be useful clinically and pathologically. In general, small round cell sarcomas are more commonly found in children, while pleomorphic and myxoid sarcomas arise almost exclusively in adults. Spindle

cell sarcomas and epithelioid/polygonal sarcomas are most often observed in young to middle-aged adults. Nevertheless, as would be expected, limitations exist regarding this form of classification. Certain tumors, such as embryonal rhabdomyosarcoma (ERMS), may show a wide range of cytomorphic features, with some examples displaying predominantly small cell morphologic features and others containing a prominent spindle cell component. Furthermore, some examples of ERMS may contain a prominent myxoid stroma and could be appropriately considered in the differential diagnosis of myxoid sarcomas. The cytologic features of synovial sarcoma and clear cell sarcoma may be arguably placed into the spindle cell or epithelial/polygonal cell groups. Despite the imperfections inherent in this classification system, we believe that such a categorization is often helpful, at least as a starting point, for narrowing the differential diagnosis for an individual soft tissue sarcoma specimen.

The Importance of Ancillary Studies

With the exception of adult pleomorphic sarcomas, at our institution, specific treatment protocols are initiated based on histologic subtype (eg, rhabdomyosarcoma and Ewing’s sarcoma) and tumor grade. For this reason, we routinely obtain FNAB material for processing as a “histologic” cell block. A concomitantly obtained percutaneous needle core biopsy may be used in a similar fashion. The latter often allows for more accurate determination of the “line of differentiation” or histologic subtype of the soft tissue tumor in question, providing a potential source for ancillary studies if deemed necessary. In a similar fashion, aspirated material also may be preserved in glutaraldehyde for electron microscopic analysis. Suspected cases of extranodal malignant lymphoma manifesting in soft tissue may be confirmed and immunophenotyped by flow cytometry by using FNAB material and RPMI media.

In most cases of suspected soft tissue sarcoma and all pediatric tumors, we routinely determine DNA ploidy by image analysis. Image analysis may be performed on histologic sections of a cell block, cytologic smears on specially prepared

slides, or both. Not only have we found this technique more sensitive than flow cytometry for the detection of aneuploidy, but we also have found image analysis especially useful as a diagnostic aid in the histologic subtyping of pediatric soft tissue sarcomas. In our experience, ERMSs are virtually always hyperdiploid, while alveolar rhabdomyosarcomas (ARMSs) are usually tetraploid.⁶ We have encountered 2 examples of intra-abdominal desmoplastic small round cell tumor (DSRCT), both of which were diploid by image analysis. Interestingly, 1 of these cases was initially misdiagnosed as rhabdomyosarcoma owing to diffuse and strong immunopositivity for desmin and myosinlike filaments by electron microscopy. As diploidy is a rare finding in rhabdomyosarcomas but is commonly observed in intra-abdominal DSRCTs,⁷ determining

Table 2
Classification of Soft Tissue Sarcomas Based on Predominant Cytomorphologic Features

Small Round Cell	Rhabdomyosarcoma, embryonal and alveolar
	Ewing’s sarcoma
	Neuroblastoma
	Mesenchymal chondrosarcoma
	Desmoplastic small round cell tumor
Spindle Cell	Fibrosarcoma
	Leiomyosarcoma
	Synovial sarcoma
	Malignant peripheral nerve sheath tumor
	Hemangiopericytoma
Epithelioid/Polygonal Cell	Epithelioid sarcoma
	Epithelioid hemangioendothelioma/angiosarcoma
	Epithelioid malignant schwannoma
	Alveolar soft part sarcoma
	Clear cell sarcoma
Pleomorphic	Malignant fibrous histiocytoma
	Pleomorphic liposarcoma
	Pleomorphic leiomyosarcoma
	Pleomorphic rhabdomyosarcoma
	Extraskeletal osteosarcoma
	Angiosarcoma
Myxoid	Myxofibrosarcoma
	Myxoid liposarcoma
	Myxoid chondrosarcoma

Table 1
Clinical, Radiologic, and Pathologic Features of Benign vs Malignant Soft Tissue Lesions

Feature	Benign	Malignant
Size	Small, often well-circumscribed	Large, often infiltrative
Location	Superficial and/or cutaneous	Deep and/or intramuscular
Cellularity	Slight to moderately cellular, rarely hypercellular	Moderately to markedly cellular
Cohesion	Tendency to form cohesive tissue fragments, less commonly single cells	Tendency toward discohesiveness with abundant dissociated single cells
Nuclei	Uniform size, “open” or vesicular chromatin pattern	Often pleomorphic and variable in size; coarse chromatin pattern
Necrosis	Usually absent	Often present

DNA ploidy by image analysis appears to represent a useful diagnostic clue to pursue a diagnosis of the much less common DSRCT, especially in small biopsy specimens such as FNAB.

When deemed necessary, we have combined FNAB-aspirated material and RPMI 1640 tissue culture media for subsequent cell culture and cytogenetic analysis. By using this approach, we have successfully confirmed 3 examples of synovial sarcoma with its classic translocation, t(X;18)(p11;q11) and 1 case of Ewing's sarcoma, t(11;22)(q24;q12). Unfortunately, the low sensitivity of this technique and the time required for positive results, which in low-grade malignant tumors may be 1 to 2 weeks, limits its usefulness. Although we have no personal experience with some of the newer techniques, the use of cell block material for the detection of specific DNA sequences using hybridization with complementary DNA probes (fluorescent in situ hybridization) may prove more sensitive and practical for cytogenetic analysis. The most specific techniques probably encompass detection of chimeric messenger RNA by reverse transcriptase–polymerase chain reaction. Recently, European investigators successfully used reverse transcriptase–polymerase chain reaction on archival FNAB smears to detect the EWS/FLI-1 fusion transcription of Ewing's sarcoma.⁸ Unfortunately, the sensitivity of the technique was low (58%).

Specific Histologic Types of Sarcomas

Rhabdomyosarcoma

Rhabdomyosarcoma represents the most common soft tissue sarcoma of childhood. Histologically, childhood

rhabdomyosarcoma shows a wide range of morphologic appearances but can usually be subtyped into 2 general categories—embryonal (ERMS) and alveolar (ARMS). A superior prognosis is associated with the botryoid and spindle cell forms of ERMS, an intermediate prognosis with conventional ERMS, and a generally poor prognosis with ARMS.⁹ Importantly, the subclassification of rhabdomyosarcoma is based on morphologic criteria and does not incorporate immunohistochemical, cytogenetic, or molecular genetic analysis.⁹ Regardless of subtype, FNAB reveals most examples of rhabdomyosarcoma to be characterized by moderately to highly cellular smears consisting mostly of individually dispersed malignant cells. In general, the degree of cytologic variability tends to exceed that of other small round cell sarcomas. More specifically, FNAB specimens of ERMS are usually composed of small to intermediate-sized cells with round to polygonal or even spindled contours. Nuclei are generally round to oval and hyperchromatic and may have 1 or more prominent nucleoli. Depending on the degree of differentiation, scant to abundant amounts of dense cytoplasm may be present, and rarely cross-striations are evident **Image 1**.^{10,11} Less commonly, ERMS may contain abundant amounts of myxoid stroma, manifested in cytologic preparations as metachromatic stromal fragments **Image 2**.

In comparison with ERMS, ARMS is composed of a population of larger, more uniformly round to polygonal cells usually with a thin rim of dense cytoplasm. A helpful diagnostic feature of ARMS is the presence of multinucleated tumor giant cells **Image 3**. Infrequently, ERMS and ARMS may display a frothy background (tigroid appearance) reminiscent of that seen in germinomas **Image 4**.¹⁰

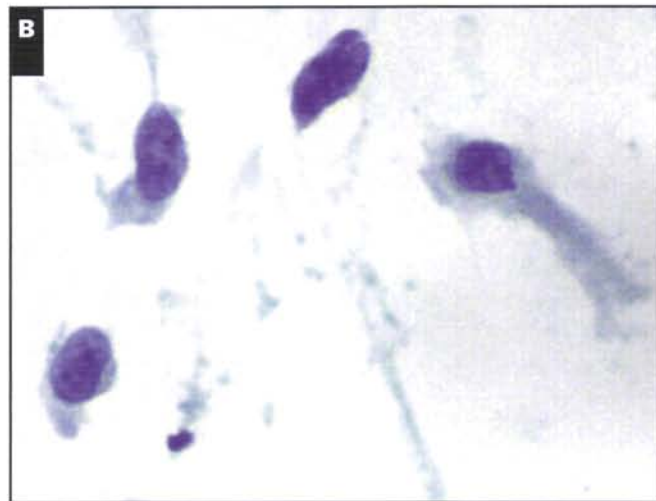
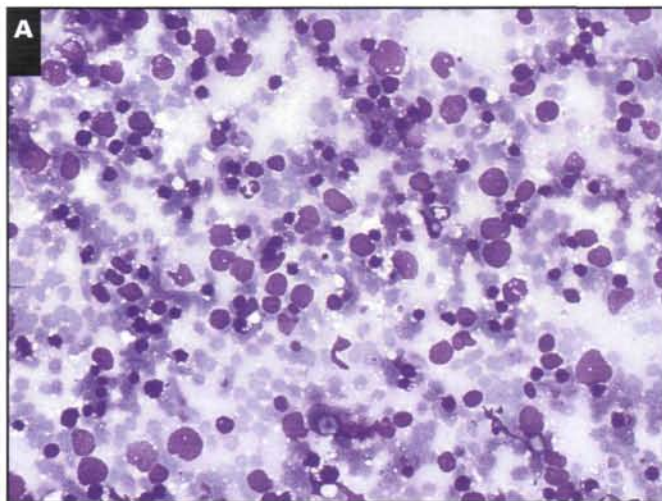


Image 1 Embryonal rhabdomyosarcoma characterized by a wide spectrum of cytomorphologic variability ranging from primitive-appearing small blue cells with hyperchromatic nuclei and irregular contours to more differentiated rhabdomyoblasts with abundant dense cytoplasm (A, rapid Romanowsky, $\times 200$; B, Papanicolaou, $\times 1,000$).

Despite the seemingly distinct morphologic differences between ARMS and ERMS in cytologic smears, in our experience and in that of others, extensive cytomorphologic overlap exists between the 2 subtypes, making absolute distinction often difficult to impossible.¹⁰ In these circumstances, determination of DNA ploidy by image analysis may be a useful adjunct. ERMS are usually hyperdiploid, while ARMS are almost always at least tetraploid.⁶ Cytogenetic analysis also may be helpful, because the majority of cases of ARMS have a specific translocation, t(2;13)(q35;q14). Nevertheless, for initial therapy purposes, it is more important that the pathologist confirm the tumor as a rhabdomyosarcoma than specify its histologic subtype. Positive immunostaining for desmin, muscle-specific actin, myo-D1, and/or myogenin helps support the diagnosis of rhabdomyosarcoma. Electron microscopy on aspirated cellular material will usually demonstrate at least rudimentary myoid differentiation with the presence of thick and thin filaments and/or Z-band material.

Ewing's Sarcoma and PNET

Ewing's sarcoma and primitive neuroectodermal tumor (PNET) represent a family of similar-appearing bone and soft tissue sarcomas all of which usually share the same cytogenetic abnormality, t(11;22). Historically, the distinction of Ewing's sarcoma from PNET rested largely on the finding of a significant but rather arbitrary number of rosettes, usually present in PNET but absent in Ewing's sarcoma. Most investigators now consider Ewing's sarcoma and PNET to represent points along a continuous spectrum of the same neoplasm, with classic undifferentiated Ewing's

sarcoma at one end and fully developed PNET with clear-cut neural differentiation at the opposite end.¹²

Similar to rhabdomyosarcoma, aspirates from Ewing's sarcomas yield highly cellular smears dominated by mostly individually dispersed cells and scattered small cohesive clusters. The neoplastic cells are strikingly uniform, possessing a single round nucleus with a finely granular chromatin pattern and an extraordinarily high nuclear/cytoplasmic ratio with only a thin rim of cytoplasm. Nucleoli are inconspicuous to absent **Image 5**.¹³ Small intracytoplasmic vacuoles are often present, indicative of glycogen. The latter finding is

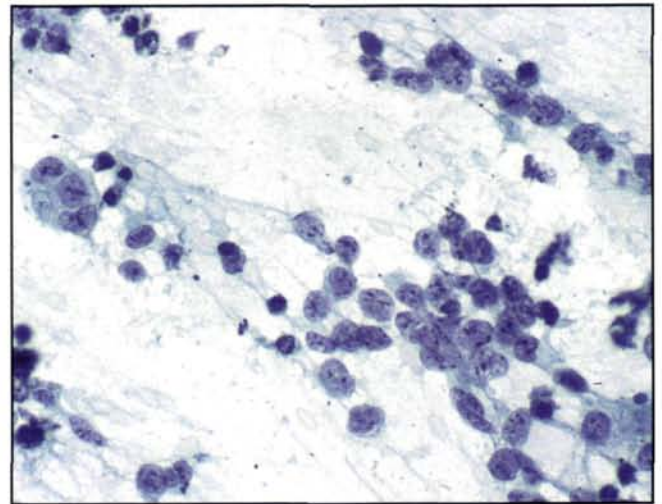


Image 3 Alveolar rhabdomyosarcoma characterized by a mostly uniform population of large ovoid-to-round tumor cells. Note the multinucleated tumor giant cell (upper left) (Papanicolaou, $\times 200$).

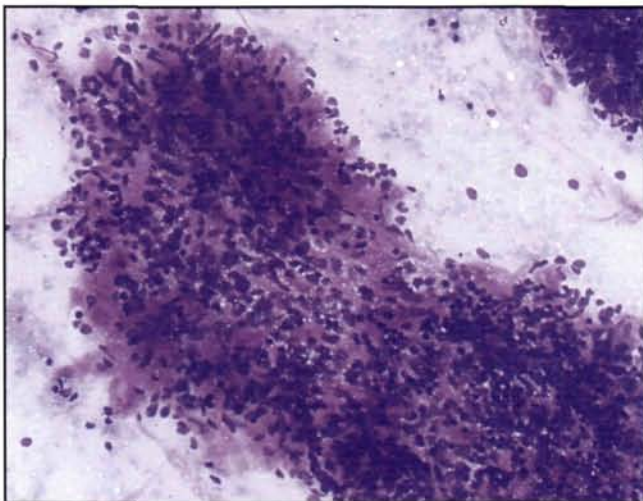


Image 2 Myxoid embryonal rhabdomyosarcoma exhibiting a large, myxoid cohesive stromal fragment (rapid Romanowsky, $\times 40$).

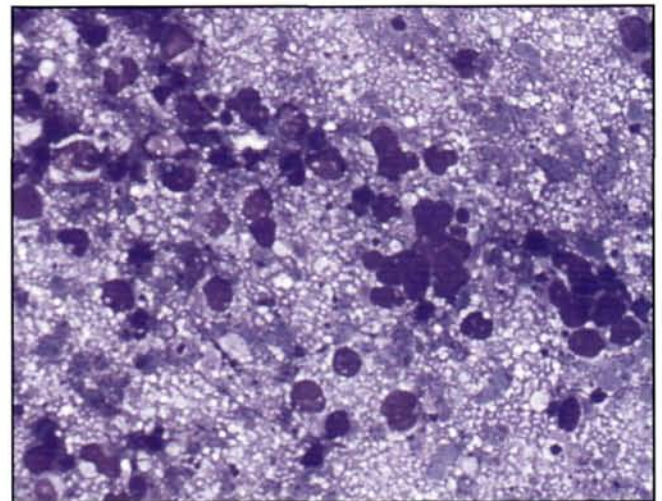


Image 4 Rarely, rhabdomyosarcomas may exhibit a frothy, bubbly background reminiscent of that seen in cytologic smears of germinomas (rapid Romanowsky, $\times 200$).

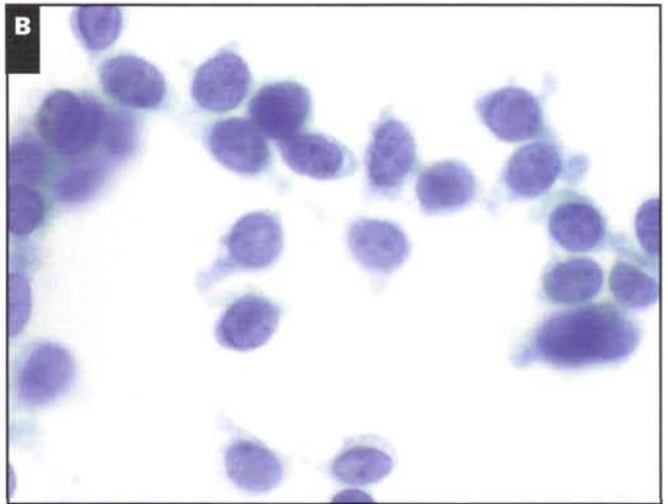
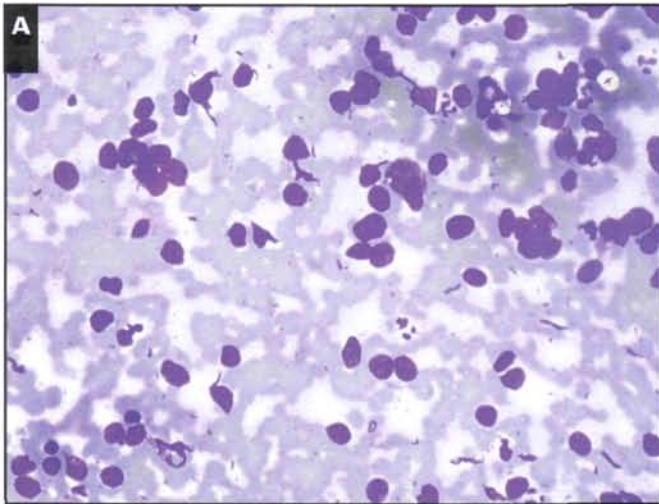


Image 5 Ewing's sarcoma characterized by a mostly uniform population of round to ovoid cells with high nuclear/cytoplasmic ratios and arranged mostly singly and in small cohesive clusters. Nuclear pleomorphism is not significant (A, rapid Romanowsky, $\times 200$; B, Papanicolaou, $\times 600$).

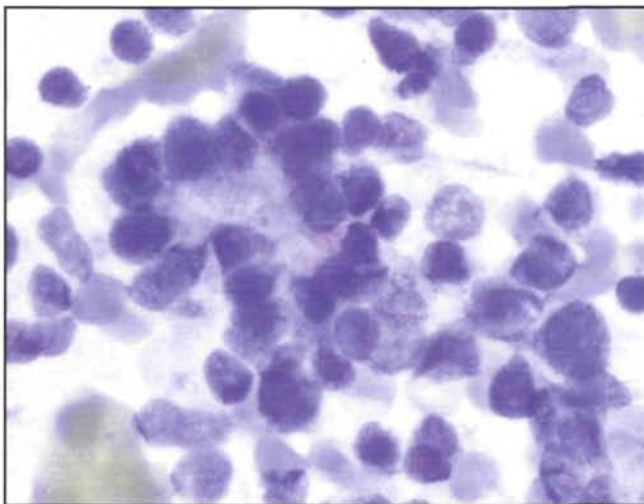


Image 6 Ewing's sarcoma (primitive neuroectodermal tumor) with characteristic pseudorosette, a very rare finding in cytologic smears (rapid Romanowsky, $\times 400$).

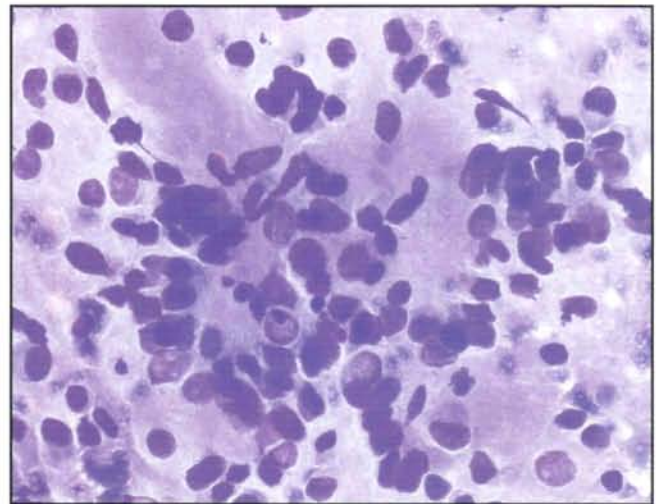


Image 7 Neuroblastoma composed of a mixed population of primitive small blue cells and more differentiated cells with eccentric dense cytoplasm. Note the background metachromatic neurofibrillary material (rapid Romanowsky, $\times 200$).

relatively nonspecific, as other similar small round cell tumors (eg, rhabdomyosarcoma and malignant lymphoma) also may contain variable amounts of intracytoplasmic glycogen. A more specific but relatively uncommon finding is the presence of pseudorosette formation **Image 6**. Rarely, Ewing's sarcomas may display uniformly enlarged nuclei with significant membrane irregularities and occasional prominent nucleoli.¹³ Such variants have been referred to as atypical (large cell) Ewing's sarcoma.

Ancillary diagnostic studies are helpful and, in most cases, essential for establishing a specific diagnosis.

Immunohistochemically, virtually all cases of the Ewing's sarcoma family possess the mic-2 glycoprotein product as demonstrated by staining for the monoclonal antibody O13(CD99).¹⁴ Ultrastructural features are rather nonspecific and include intracytoplasmic glycogen, primitive intercellular junctions, and uniformly distributed nuclear euchromatin. Cytogenetic analysis may reveal a variety of translocations involving the Ewing's sarcoma gene on chromosome 22, including the most common translocation, $t(11:22)(q24;q12)$ followed in decreasing order of frequency by $t(21;22)(q12;q12)$, and $t(7;22)(q22;q12)$.^{15,16} The characteristic

t(11:22) translocation with the EWS/FLI-1 fusion transcript should not be considered entirely specific for Ewing's sarcoma because other soft tissue sarcomas, such as ERMS and ARMS and polyphenotypic tumor of childhood, also reportedly have contained this genotype.^{17,18}

Neuroblastoma

Neuroblastoma is the third most common malignant tumor of childhood, with most examples diagnosed before 5 years of age.^{19,20} Although most cases arise from the adrenal gland and retroperitoneum, neuroblastomas may occur anywhere along the sympathetic chain, including the mediastinum. Prognosis tends to correlate with age at diagnosis, primary site, stage, and degree of cellular differentiation.²⁰ Determination of DNA ploidy by image analysis represents a useful prognostic indicator, as diploid tumors tend to behave more aggressively than aneuploid tumors.²¹

FNAB of neuroblastoma generally yields hypercellular smears with mostly discohesive malignant small blue cells and scattered cohesive aggregates. Within the latter, nuclear molding and, less commonly, Homer Wright rosettes may be evident. Overall, the neoplastic cells tend to be relatively uniform with mostly round to ovoid nuclei, a finely granular nuclear chromatin pattern, and a high nuclear/cytoplasmic ratio. A useful diagnostic feature is the presence of fibrillary matrix (neuropil) that may be seen in rapid Romanowsky-stained and Papanicolaou-stained material **Image 7**.²² Depending on the degree of differentiation, schwannian-type spindle-shaped cells and binucleated and multinucleated ganglion cells also may be present **Image 8**.²² Necrotic debris and dystrophic calcifications are sometimes observed. As with all small blue cell sarcomas of childhood, ancillary studies are helpful for establishing a definitive diagnosis. Immunohistochemically, most examples of neuroblastoma express neuron-specific enolase, synaptophysin, and S-100 protein but are uniformly negative for the monoclonal antibody O13(CD99).¹⁴ Electron microscopic examination of neuroblastoma shows intracytoplasmic, dense core, neurosecretory-type granules and abundant dendritic processes containing microtubules.

Extraskelletal Mesenchymal Chondrosarcoma

Mesenchymal chondrosarcoma (MC) is a bimorphic tumor generally composed of primitive-appearing, small blue cells and islands of metaplastic cartilage. Most cases occur in young adults and more commonly arise within the skeleton, principally the jaws and ribs, than the

extraskelletal soft tissues. Within the latter, the principal anatomic sites include the head and neck, cranial and spinal dura mater, and deep soft tissues of the lower extremities.²³

Cytologic smears from cases of MC often bear a striking resemblance to those seen with Ewing's sarcoma, being composed of mostly uniform, round to ovoid tumor cells with inconspicuous nucleoli and scant cytoplasm.²⁴ We do not believe, based on cytomorphologic analysis alone, that MC can be reliably distinguished from Ewing's sarcoma. Only the presence of identifiable matrix material (eg, cartilage) can establish a diagnosis of MC.²⁴ Furthermore, some examples of MC reportedly have expressed, immunohistochemically, the monoclonal antibody O13(CD99).²⁵ Needle core biopsy and incisional biopsy probably represent better techniques for establishing a diagnosis of MC.

Desmoplastic Small Round Cell Tumor

DSRCT is a relatively recently described entity, arising predominantly within the abdomen and generally afflicting young adults between the ages of 15 and 35 years.⁷ FNAB samples are variably cellular, depending on the prominence of the desmoplastic stroma within the tumor. The neoplastic cells tend to be mostly uniform, round to ovoid, and arranged individually and within small aggregates. Nuclei have a finely granular chromatin pattern and inconspicuous nucleoli.⁵ Unfortunately for the cytopathologist, the neoplastic cells closely resemble those seen in Ewing's sarcoma **Image 9**. A useful finding in some FNAB specimens is the presence of scattered, variably cellular, collagenous stromal fragments, a feature not observed with Ewing's sarcoma.⁵ Immunohistochemically, DSRCT usually shows evidence of multipotential

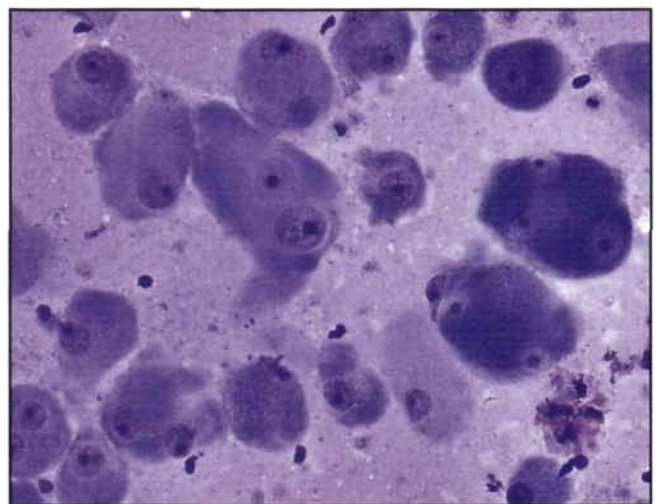


Image 8 Ganglioneuroblastoma with numerous ganglion cells (rapid Romanowsky, $\times 200$).

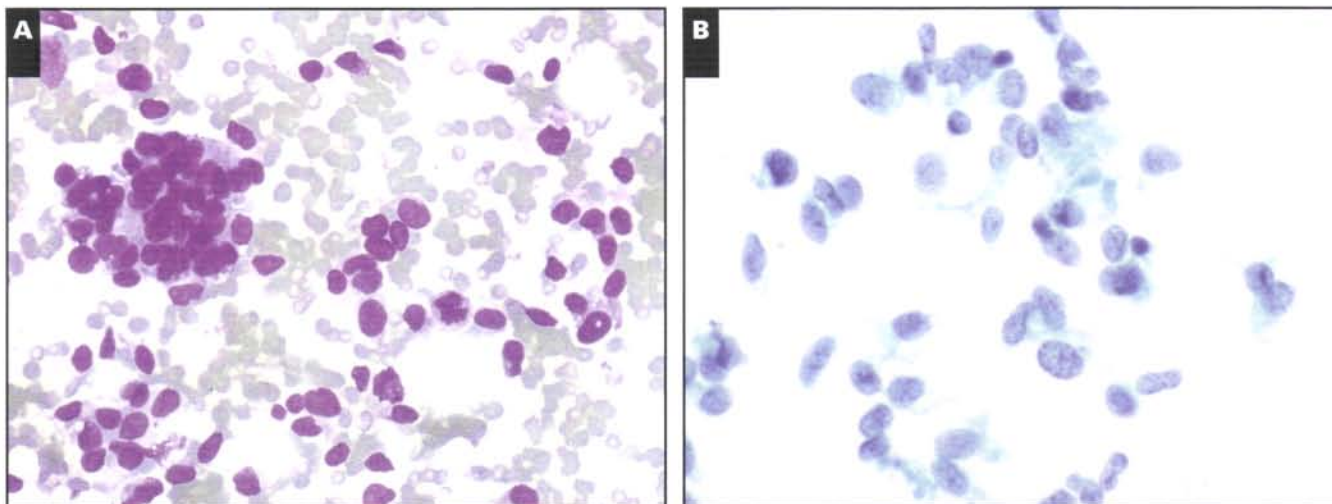


Image 9 Desmoplastic small round cell tumor characterized by a uniform population of round to ovoid neoplastic cells with finely granular nuclear chromatin, inconspicuous nucleoli, and high nuclear/cytoplasmic ratios (A, rapid Romanowsky, $\times 100$; B, Papanicolaou, $\times 400$).

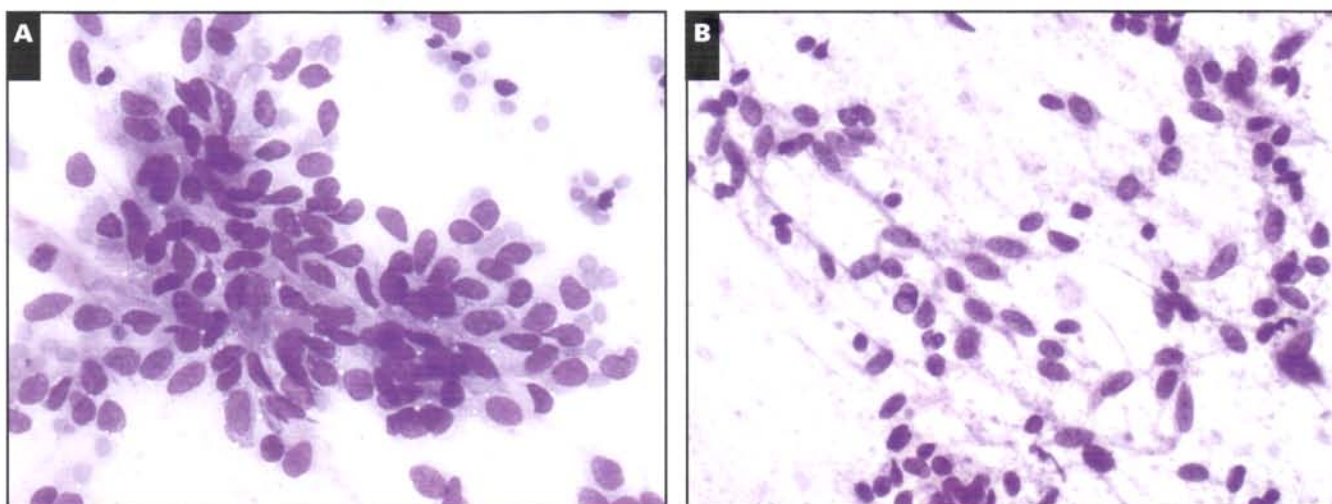


Image 10 Synovial sarcoma with aggregates and discohesive ovoid to spindle tumor cells with ovoid, hyperchromatic nuclei, inconspicuous nucleoli, and scant tapering cytoplasm (A, rapid Romanowsky, $\times 200$; B, Papanicolaou, $\times 400$) (Reproduced from Kilpatrick SE, Teot LA, Stanley MW, et al. Fine needle aspiration biopsy of synovial sarcoma: a cytomorphologic analysis of primary, recurrent, and metastatic tumors. *Am J Clin Pathol.* 1996;106:769–775.)

differentiation, expressing multiple immunohistochemical markers, including cytokeratins, neuroendocrine markers, and desmin.⁷ We recently encountered a case of intra-abdominal DSRCT initially misdiagnosed on FNAB as rhabdomyosarcoma because of immunohistochemical and ultrastructural evidence of myoid differentiation. Owing to its highly aggressive biologic nature and less than adequate response to multidisciplinary therapy, DSRCT should be distinguished from other small round cell sarcomas of childhood.⁷ When immunohistochemical studies are equivocal, determination of DNA ploidy by image analysis is a helpful diagnostic aid.

Most examples of DSRCT are diploid; in contrast, most rhabdomyosarcomas are aneuploid.^{6,7} Cytogenetic analysis in up to 75% of cases reveals a translocation involving the *EWS* gene on chromosome 22, $t(11;22)(p13;q12)$ with the *WT1/EWS* fusion gene product.⁷

Synovial Sarcoma

Synovial sarcomas are relatively rare tumors, usually arising near or adjacent to a joint cavity and generally

afflicting young adults. Histologically, 3 distinct subtypes are recognized—biphasic, monophasic fibrous, and monophasic epithelial. The first 2 subtypes are relatively common and occur at approximately equal frequency; the third subtype, monophasic epithelial, is extraordinarily rare.

On FNAB, the monophasic fibrous and biphasic subtypes of synovial sarcoma yield moderate to highly cellular smears composed of a mostly individually dispersed, uniform population of ovoid to slightly spindled cells with ovoid hyperchromatic nuclei, high nuclear/cytoplasmic ratios, and scant tapering cytoplasm.²⁶ Small aggregates of tumor cells also may be evident. Nucleoli are small to inconspicuous **Image 10**. Nuclear pleomorphism is not a prominent feature and, if present, should cause reassessment of the diagnosis. Despite the rather distinct epithelial component in biphasic synovial sarcoma, in our experience and that of others, the presence of identifiable epithelial cells in cytologic smears is a relatively rare finding.^{26,27} In comparison with the spindled cells, the epithelial cells are typically larger, have more rounded nuclear contours, and may display abundant amounts of minutely vacuolated cytoplasm **Image 11**. Immunohistochemically, the fibrous and epithelial portions usually express cytokeratin and epithelial membrane antigen. Synovial sarcoma also frequently shows cytoplasmic expression for the Ewing's sarcoma marker, O13 (CD99).²⁸ The latter finding has important prognostic implications, as some examples of synovial sarcoma are poorly differentiated and morphologically resemble Ewing's sarcoma/PNET-type tumors. Cytogenetic analysis in more than 90% of cases of synovial sarcoma reveals a characteristic translocation, t(x;18)(p11;q11) with the SYT-SSX fusion gene product.²⁹

The differential diagnosis of synovial sarcoma includes fibrosarcoma, a diagnosis that has been the subject of much recent critical review.^{30,31} Most neoplasms diagnosed in the past as fibrosarcoma would, by using our current histologic and ancillary techniques, be classified as malignant fibrous histiocytomas (MFHs), monophasic fibrous synovial sarcomas, malignant peripheral nerve sheath tumors, or other benign and malignant lesions.³¹ Not surprisingly, the diagnosis of fibrosarcoma has become exceedingly rare. Indeed, we have not encountered any bonafide examples of fibrosarcoma examined by FNAB. By using FNAB, 1 of our cases of monophasic fibrous synovial sarcoma was initially misdiagnosed as fibrosarcoma.²⁶

Malignant Peripheral Nerve Sheath Tumor

Malignant peripheral nerve sheath tumor (MPNST), previously known as malignant schwannoma or neurofibrosarcoma, usually occurs in young to middle-aged adults and, by

definition, is associated with a large peripheral nerve trunk or a preexisting neurofibroma, and/or it may arise in a patient with neurofibromatosis.^{32,33} Because examples of MPNST with accepted histomorphologic features also may occur outside these clinical settings, establishing a definitive diagnosis may prove exceedingly difficult, even when adequate tissue samples (eg, from incisional biopsies) are obtained.

Within the spindle cell sarcoma category, MPNST probably shows the greatest cytomorphologic variability.³⁴ Monophasic synovial sarcomas tend toward extreme uniformity. FNAB specimens of MPNST are moderately to highly cellular and composed of mostly individually dispersed large neoplastic cells ranging from round and ovoid to serpentine and buckled, often with high nuclear/cytoplasmic ratios and scant amounts of tapering cytoplasm **Image 12**. Multinucleated anaplastic tumor giant cells, a feature never seen with synovial sarcomas, are commonly observed in MPNSTs.³⁴ In contrast, benign nerve sheath tumors are characterized by large, cohesive, "ropy" tumor fragments and less frequently contain solitary tumor cells **Image 13**.³⁵ Unfortunately, rhythmic palisading of the elongated tumor nuclei in parallel rows suggestive of nerve sheath differentiation is rarely observed in the cytologic smears of MPNST. Although most cases of MPNST are easily identified as malignant, establishing its nerve sheath origin requires clinical or radiologic correlation or both. A potential diagnostic pitfall is inadvertent FNAB sampling of a coexisting benign nerve sheath tumor, "missing" the prognostically important malignant component. In a similar fashion, low-grade MPNSTs may also be misdiagnosed as benign by FNAB owing to their significant

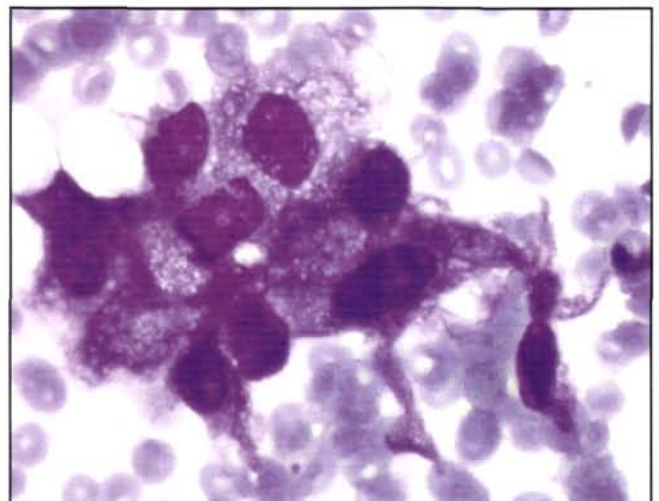


Image 11 Only rarely in biphasic synovial sarcomas are these larger epithelial cells visualized, displaying abundant amounts of minutely vacuolated cytoplasm (rapid Romanowsky, $\times 600$). (Reproduced by permission from Kilpatrick et al.²⁶)

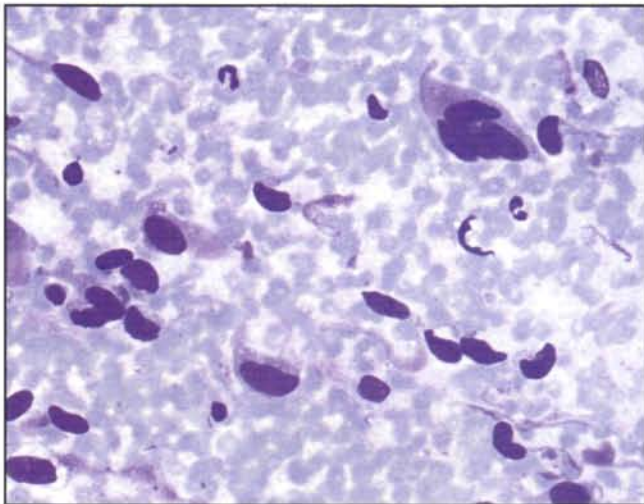


Image 12 Malignant peripheral nerve sheath tumor characterized by large, mostly discohesive, ovoid to spindled tumor cells with hyperchromatic nuclei and dense tapering cytoplasm. Note the multinucleated tumor giant cell (upper center right) (rapid Romanowsky, $\times 200$).

cytomorphologic overlap with benign nerve sheath tumors. For these reasons, any lesion clinically suggestive of malignancy, even in the presence of a “benign” FNAB specimen, requires further investigation.^{34,35}

Immunohistochemically, many examples of MPNST express S-100 protein, usually in a focal and patchy manner, but up to 50% of cases may be negative for S-100 protein.^{36,37} Diffuse and strong immunopositivity for S-100 protein is more commonly observed with benign nerve sheath tumors.³⁷ Some similar appearing sarcomas (eg, synovial sarcoma) may focally express S-100 protein.³⁸ As a consequence, meticulous attention to cytomorphologic and clinicoradiologic features and, when available, a panel of immunohistochemical markers is essential for a specific FNAB diagnosis of MPNST. Ancient changes within a benign nerve sheath tumor may also cause diagnostic confusion. Nevertheless, if careful attention is paid to other cytomorphologic and clinical features, separation of ancient changes in a benign nerve sheath tumor from MPNST is usually (but not always) possible.

Hemangiopericytoma

Cytologically, the differential diagnosis of spindle cell sarcomas must include malignant hemangiopericytoma. However, as the hemangiopericytoma vascular pattern may be present in a variety of tumors, including synovial sarcoma and malignant peripheral nerve sheath tumor, establishing a definitive diagnosis may be difficult or

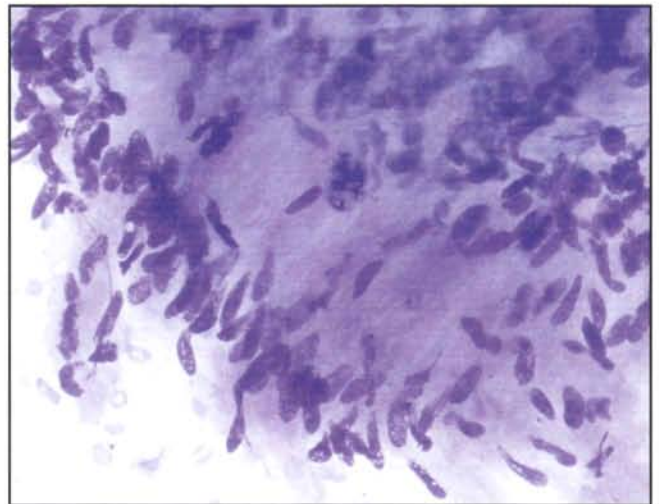


Image 13 In contrast to malignant peripheral nerve sheath tumor, fine-needle aspiration biopsy specimens from benign nerve sheath tumors yield smaller spindled to serpentine cells arranged in large cohesive tissue fragments. Note the nuclear palisading (rapid Romanowsky, $\times 300$).

impossible. In fact, some investigators have questioned whether hemangiopericytoma has been overdiagnosed in the past.³⁹ Most examples occur in middle-aged adults and arise within the pelvis, retroperitoneum, and lower extremities.⁴⁰ FNAB specimens are relatively hypercellular and composed of a uniform population of ovoid to spindled cells closely resembling those seen in synovial sarcoma. Significant nuclear pleomorphism is not present.⁴¹ Without a concomitantly obtained cell block, the characteristic vascular pattern is not generally observed in cytologic preparations. Unfortunately, vimentin represents the only consistently positive immunohistochemical marker of hemangiopericytoma.⁴² We consider the diagnosis of hemangiopericytoma to represent one of exclusion and do not believe that it can be reliably diagnosed by FNAB.

Clear Cell Sarcoma

Clear cell sarcoma, also known as malignant melanoma of soft parts, is a relatively rare soft tissue sarcoma that, as the name implies, morphologically resembles malignant melanoma but tends to arise within the deep soft tissues of the extremities, principally the foot and ankle. Most patients are young adults between the ages of 20 and 40 years.⁴³

FNAB yields moderately cellular aspirates composed of a mostly discohesive and uniform population of ovoid to fusiform-appearing cells with vesicular nuclei and a single prominent nucleolus. Cytoplasm may be scant to abundant but generally stains clear to pale **Image 14**.⁴⁴ Multinucleated

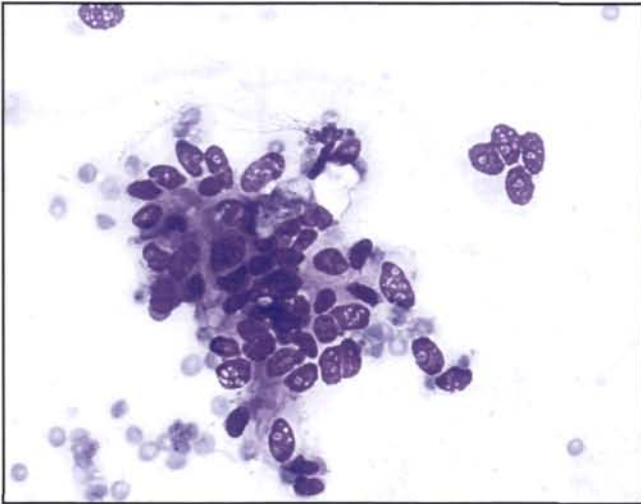


Image 14 Clear cell sarcoma characterized by mostly uniform, ovoid tumor cells with scant to clear granular cytoplasm, vesicular nuclei, and a single prominent nucleolus (rapid Romanowsky, $\times 200$).

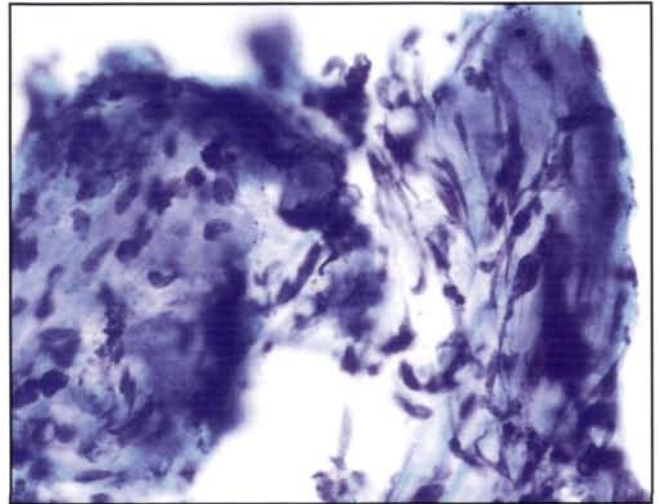


Image 15 Leiomyosarcoma characterized by closely packed spindle-shaped tumor cells arranged in parallel fascicles in a cohesive tissue fragment (Papanicolaou, $\times 200$).

giant cells with nuclei arranged peripherally in a wreathlike pattern are a rare but helpful finding. Intranuclear cytoplasmic pseudoinclusions and intracytoplasmic melanin, in our experience, are extraordinarily rare features in cytologic smears. As with malignant melanoma, the neoplastic cells in clear cell sarcoma commonly show immunopositivity for S-100 protein but less often with the melanoma-associated antigen, HMB-45.⁴³ Cytogenetic analysis has revealed a consistent translocation involving chromosomes 12 and 22, $t(12;22)(q13;q12)$ with the ATF1-EWS fusion product.²⁹

Leiomyosarcoma

Leiomyosarcoma is a tumor of adult patients, most commonly arising in areas containing abundant amounts of smooth muscle. Thus, common locations include the genitourinary region, gastrointestinal tract, and adjacent to muscular-walled blood vessels. Nevertheless, occasional examples may also occur within the deep soft tissues of the extremities and retroperitoneum.

FNAB specimens of leiomyosarcoma are usually variably cellular and, in contrast to other spindle cell sarcomas, are more often arranged in loose clusters, tissue bundles, and fascicles. Individually dispersed tumor cells are less commonly evident **Image 15**.⁵ Indeed, the presence of closely packed spindle-shaped, tumor cells in “parallel side-by-side arrangements” suggests a diagnosis of leiomyosarcoma.⁴⁵ The neoplastic cells typically have elongated, cigar-shaped, hyperchromatic nuclei with blunted to pointed ends

surrounded by abundant amounts of dense cytoplasm, sometimes containing perinuclear vacuoles.⁴⁵ Solitary “stripped” or naked tumor nuclei are common. Rarely, an epithelioid cell pattern may predominate, making distinction from carcinoma difficult **Image 16**. Such cases usually are seen arising within the gastrointestinal tract. High-grade pleomorphic tumors, which tend to be less common than low-grade tumors, are usually composed of discohesive solitary tumor cells exhibiting marked nuclear pleomorphism and accompanied by multinucleated tumor giant cells. The latter may be difficult to distinguish from malignant fibrous histiocytoma

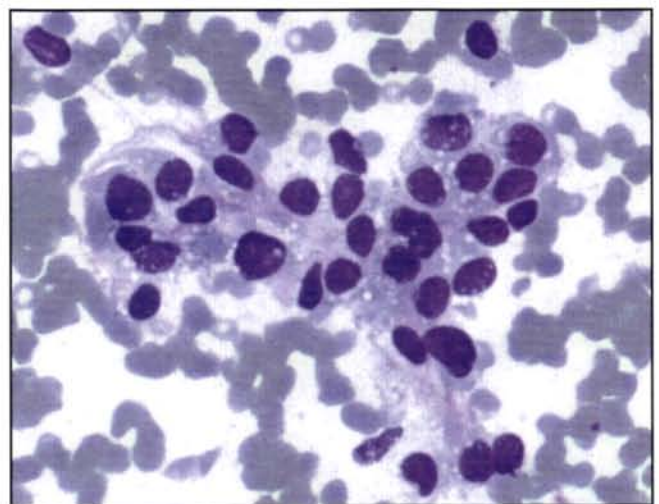


Image 16 Epithelioid leiomyosarcoma showing round to polygonal tumor cells (rapid Romanowsky, $\times 200$).

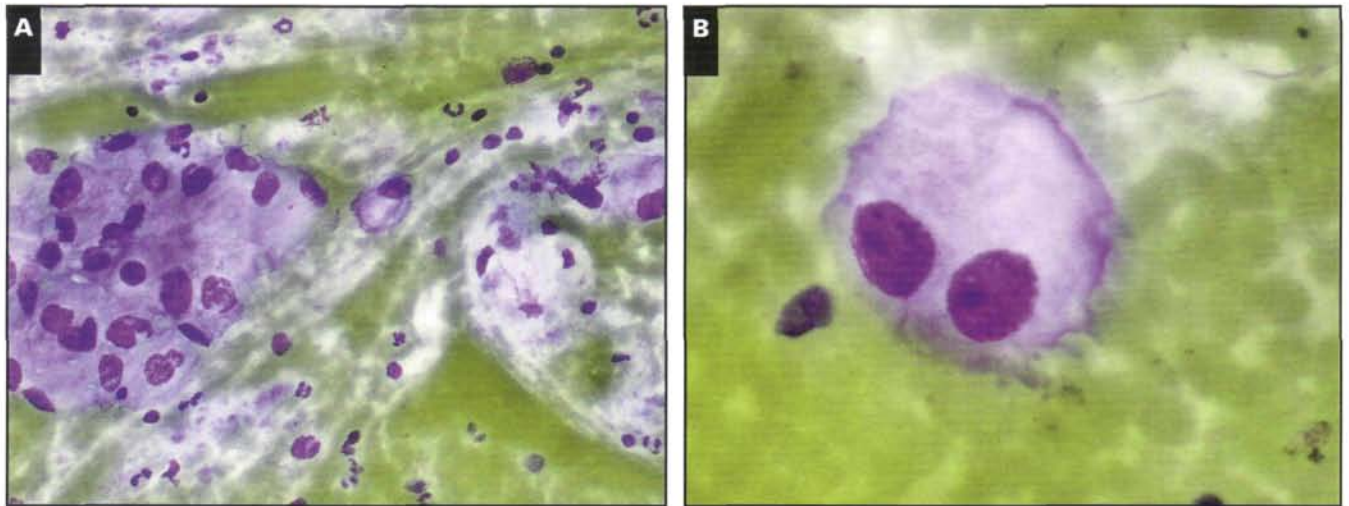


Image 17 Alveolar soft part sarcoma characterized by extraordinarily large polygonal tumor cells with eccentric nuclei and prominent nucleoli. Binucleated forms may be present (A, rapid Romanowsky, $\times 200$; B, rapid Romanowsky, $\times 400$).

(MFH). In problematic cases, immunohistochemical stains for α -smooth-muscle actin and desmin may be helpful in this distinction, although its prognostic significance is debatable. Distinguishing low-grade leiomyosarcomas from leiomyomas may be difficult to impossible based on cytologic features alone. Although mitotic counts are essential for determining benignancy vs malignancy in histologic sections, their usefulness in cytologic preparations is limited. Nevertheless, we regard the presence of even a single mitotic figure, especially in soft tissue smooth muscle tumors, as highly suggestive of malignancy.⁴⁶

Alveolar Soft Part Sarcoma

Alveolar soft part sarcoma (ASPS) is a rare but clinically and morphologically distinct soft tissue sarcoma that occurs principally in older adolescents and young adults.⁴⁷ Most cases arise in the lower extremity, especially the thigh; however, localization to the soft tissues of the head and neck is more commonly seen in infants and children.

FNAB usually yields slight to moderately cellular smears of mostly discohesive, large, round to polygonal cells.⁴⁸ Despite their relatively large size, the neoplastic cells are mostly uniform, exhibiting only slight variations in size and configuration. Nuclei are round to ovoid, vesicular, contain a prominent nucleolus, and are typically eccentrically placed, surrounded by an abundant amount of granular to dense cytoplasm **Image 17**. When available, periodic acid–Schiff stain reveals the characteristic rhomboid crystals that may also be confirmed by ultrastructural examination. There seem to be no immunohistochemical markers specific for ASPS.⁴⁷

However, some investigators have documented evidence of myoid differentiation with desmin positivity, while others have reported conflicting results.⁴⁷

The differential diagnosis of ASPS includes renal cell carcinoma, paraganglioma, and granular cell tumor, all of which lack the characteristic crystals seen in ASPS. Cytoplasmic glycogen is absent in granular cell tumors and paragangliomas.⁴ Clinically, paragangliomas do not occur as primary soft tissue tumors in the extremities.

Epithelioid Sarcoma

Epithelioid sarcoma (ES) is an extraordinarily rare soft tissue sarcoma that usually develops in young adults (younger than 30 years), commonly arising within the distal extremities, especially the hand.⁴⁹ FNAB specimens are moderately cellular and composed of discohesive and relatively uniform neoplastic cells exhibiting only mild to moderate nuclear pleomorphism. The nuclei are round, often eccentrically located, and surrounded by slight to moderate amounts of dense cytoplasm. Degenerating intracytoplasmic vacuoles also may be present, mimicking epithelioid hemangioendothelioma (EH) **Image 18**.⁵⁰

Recently, a “proximal type” of epithelioid sarcoma has been described that is characterized by large cell, epithelioid cytomorphic features, marked nuclear atypia, and the presence of rhabdoidlike cytoplasmic features.⁵¹ Like carcinomas, ES shows diffuse and strong immunopositivity for cytokeratins and epithelial membrane antigen. A useful immunohistochemical marker in the differential diagnosis of ES is CD34, which is often positive in ES but virtually

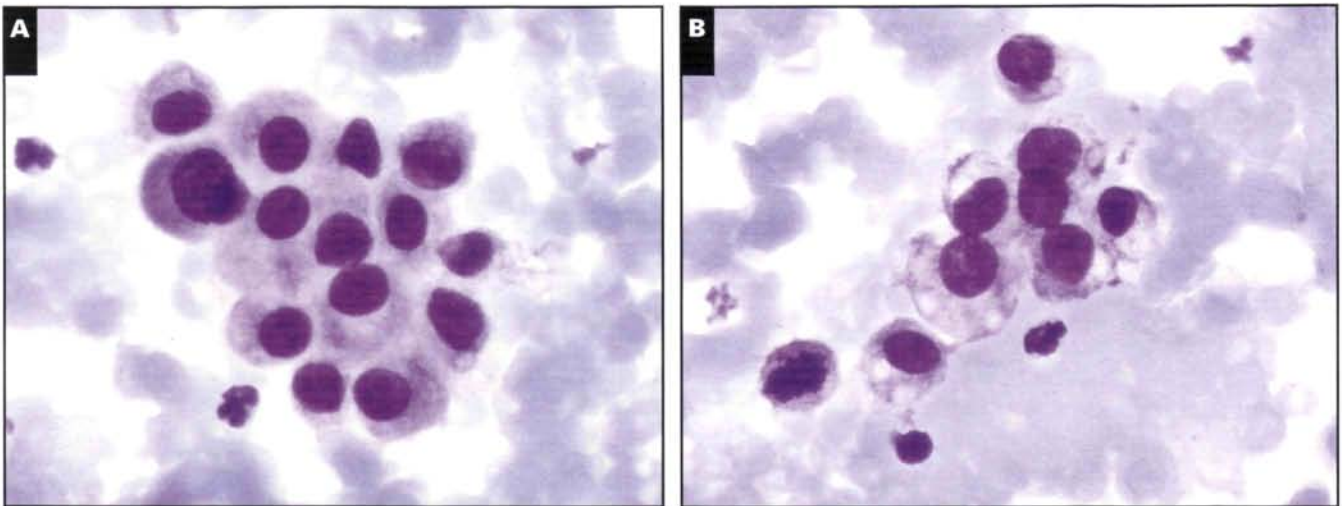


Image 18 A, Epithelioid sarcoma with round to polygonal tumor cells, ovoid to round nuclei, and an eccentric rim of mostly dense cytoplasm (rapid Romanowsky, $\times 400$). B, Occasional tumor cells may contain degenerating intracytoplasmic vacuoles, mimicking epithelioid hemangioendothelioma. Note the mitotic figure (lower left) (rapid Romanowsky, $\times 400$).

always negative in metastatic carcinomas.⁵² In contrast to EH, ES shows no immunostaining for CD31 or factor VIII.

Malignant Vascular Tumors

The term *malignant vascular tumor* encompasses the neoplasms with low-grade biologic potential, hemangioendotheliomas, as well as more clinically aggressive forms, angiosarcomas. Epithelioid hemangioendothelioma is a rare vascular tumor of borderline or “intermediate” malignant potential that may arise within bone, soft tissue, lung, liver, or

brain tissue.^{53–55} Regardless of the primary origin of the tumor, the presence of visceral involvement seems to indicate a poor prognosis.^{53,55} Indeed, EH may be multicentric involving 1 organ or anatomic area or multiple anatomic sites.⁵³

FNAB generally yields hypercellular smears composed of mostly discohesive epithelioid cells sometimes admixed with variable amounts of more spindle-shaped neoplastic cells.⁵⁶ The nuclei range from round and ovoid to polylobated and cleaved, but significant nuclear pleomorphism is not a feature of EH. Rarely, sharply demarcated intracytoplasmic vacuoles and intranuclear cytoplasmic pseudoinclusions may be evident **Image 19**.^{56,57} As mentioned, similar cytologic

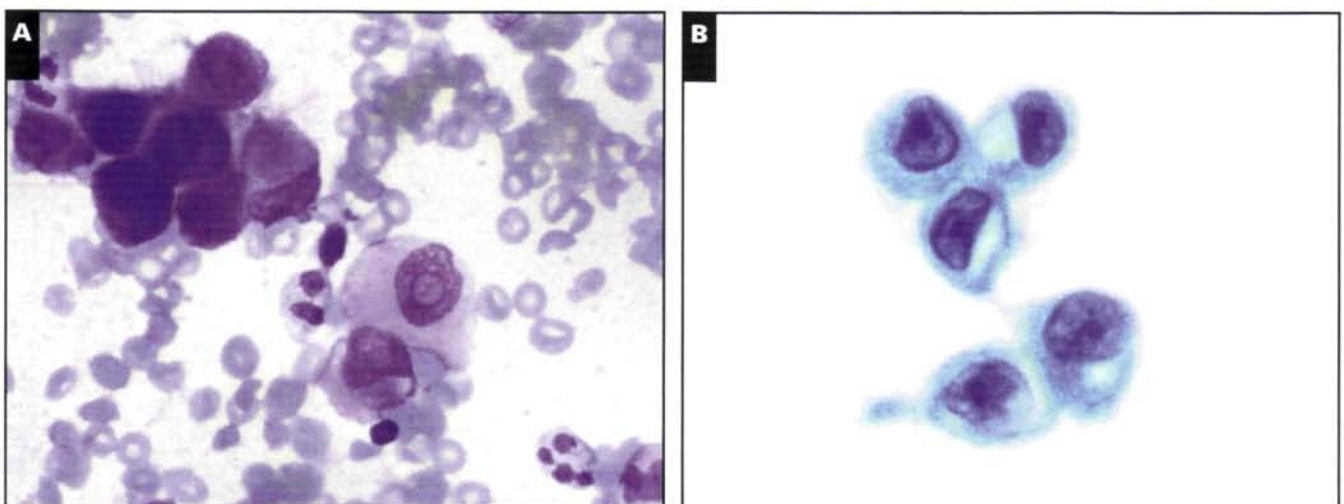


Image 19 A, Epithelioid hemangioendothelioma with round to polygonal tumor cells, ovoid, vesicular nuclei, and abundant dense cytoplasm. Note the intranuclear cytoplasmic pseudoinclusion (rapid Romanowsky, $\times 400$). B, Intracytoplasmic vacuoles, representing primitive vascular lumina, are a characteristic feature (Papanicolaou, $\times 1,000$).

features also may be observed in epithelioid sarcoma. Nevertheless, most patients with EH are older than 30 years at diagnosis, and the tumors tend to be more proximally located, often with an angiocentric distribution. Immunohistochemically, the neoplastic cells of EH show strong and diffuse positivity for CD31 and factor VIII but may occasionally express epithelial markers including cytokeratin.⁵⁵ Whether EH can be reliably separated from epithelioid hemangioma by FNAB is unclear. One of us (S.E.K.), with the aid of a cell block, recently gave a histologically confirmed diagnosis of epithelioid hemangioma of bone by FNAB.

Angiosarcomas represent high-grade malignant vascular tumors usually arising in older adults. In contrast to most pleomorphic sarcomas, cutaneous localization is more common than origin within deep soft tissues. FNAB smears are hypercellular and composed of mostly discohesive, obviously malignant cells with moderate to marked nuclear pleomorphism. In our experience, the degree of nuclear atypia, even in epithelioid variants of angiosarcoma, far exceeds the more uniform appearance of EH. Unfortunately, the cytologic findings tend to be relatively nonspecific, and vascular differentiation is usually not evident. Definitive diagnosis usually requires confirmation of vascular differentiation by ancillary studies, incisional biopsy, or both.⁵

Liposarcoma

Liposarcomas are almost exclusively tumors of adult patients that can generally be divided into 4 major histologic subtypes—well-differentiated, myxoid/round cell, pleomorphic, and dedifferentiated. Owing to their distinct

morphologic features, we address the cytologic features of each histologic subtype separately.

Well-differentiated liposarcomas usually arise within the deep soft tissues of the extremities and retroperitoneum. In our experience, the diagnosis of well-differentiated liposarcoma is not easily determined by FNAB analysis. The presence of diagnostic lipoblasts (eg, multivacuolated cells with atypical hyperchromatic and scalloped nuclei) is a helpful but unfortunately rare cytologic feature. In contrast, many cases show aggregates of adipose tissue that often do not appear reliably different from that observed in FNAB specimens of normal subcutaneous fat or conventional-appearing lipomas **Image 20**.⁵⁸ The difficulty in the diagnosis of well-differentiated liposarcoma may be further compounded by the presence of fat necrosis, which may occur alone or in association with a liposarcoma. For these reasons, we do not routinely perform FNAB on deep soft tissue lesions, which by current imaging modalities appear largely or predominantly composed of adipose tissue; if possible, performance of a percutaneous core needle biopsy is recommended. We believe that the diagnosis of well-differentiated liposarcoma is best determined with the latter or incisional biopsy material but should never preclude extensive sampling of the subsequent excisional biopsy specimen. Recent reports have indicated that most, but not all, well-differentiated liposarcomas reveal supernumerary ring or giant chromosomes by cytogenetic analysis.⁵⁹ In contrast, subcutaneous and intramuscular lipomas most often show karyotypic aberrations affecting 12q, 6p, and 13q.⁵⁹ Whether these findings can be confirmed by FNAB is unknown.

Myxoid liposarcoma, according to most series, represents the most common subtype of liposarcoma. Recent

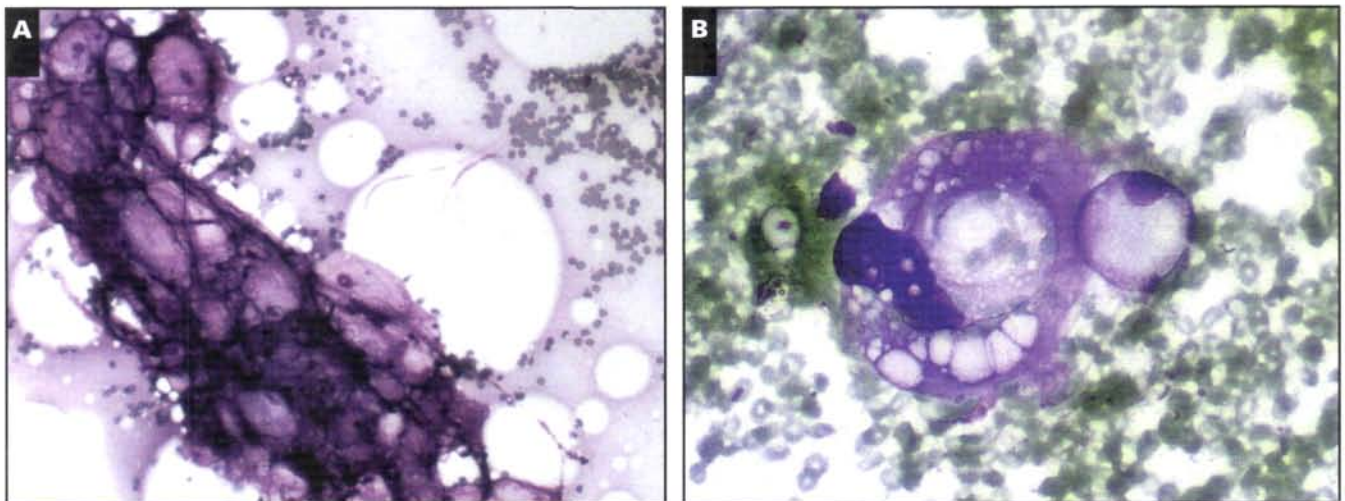


Image 20 A, Well-differentiated liposarcoma with aggregates of mostly normal-appearing adipose tissue (rapid Romanowsky, $\times 100$). B, A rare multivacuolated lipoblast with a large, irregular, and hyperchromatic nucleus (rapid Romanowsky, $\times 400$).

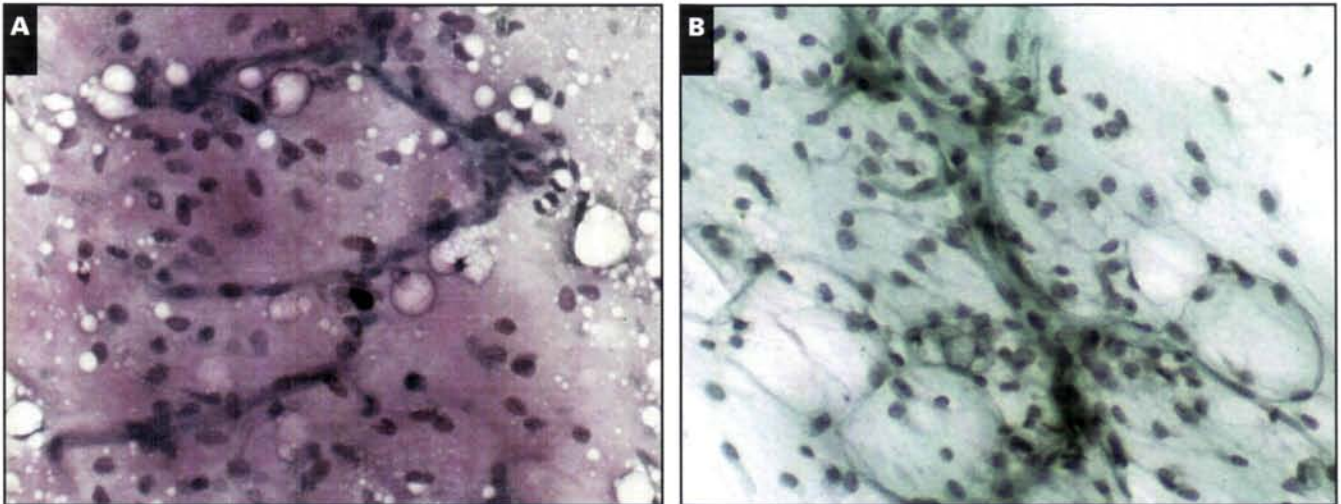


Image 21 Myxoid liposarcoma characterized by myxoid stromal fragments containing an arborizing vascular network and a mostly uniform population of ovoid to slightly spindled tumor cells. Note the occasional signet ring cell lipoblast (A, rapid Romanowsky, $\times 100$; B, Papanicolaou, $\times 200$).

evidence suggests that myxoid liposarcoma and round cell liposarcoma represent a spectrum of low- and high-grade sarcoma, respectively.^{60,61} Furthermore, myxoid and round cell liposarcoma exhibit a similar translocation in most cases, $t(12;16)(q13;p11)$.^{59,61} In its pure form, myxoid liposarcoma is characterized by the presence of a uniform population of hyperchromatic ovoid to slightly spindled-shaped cells within a prominent myxoid stroma containing an arborizing vascular network. Classic multivacuolated lipoblasts are rarely seen but so-called signet-ring cell lipoblasts are commonly observed.⁶⁰ FNAB generally yields large stromal fragments of myxoid material transversed by the arborizing capillaries and accompanied by a randomly distributed, uniform population of mostly ovoid to slightly spindled neoplastic cells **Image 21**.^{58,62} Even in the absence of classic lipoblasts, the diagnosis of myxoid liposarcoma is easily established in most cases. As myxoid liposarcoma occupies a spectrum with round cell liposarcoma, mixtures of the 2 are also commonly observed. Furthermore, as the percentage of the round cell component has prognostic significance, it is absolutely essential that the presence of even a minor round cell liposarcoma population be adequately documented.⁶⁰ Cytologically, the latter are typically larger, more rounded, and, in some cases, epithelioid with prominent nucleoli **Image 22**.

FNAB specimens of pleomorphic liposarcoma are easily recognized as malignant.⁵⁸ The smears range from slightly to moderately cellular and are composed of mostly discohesive, markedly anaplastic-appearing, pleomorphic tumor cells. In the presence of classic multivacuolated lipoblasts, the diagnosis of pleomorphic liposarcoma may be established by FNAB **Image 23**. However, in our experience, most examples lack the diagnostic lipoblasts

and are designated nonspecifically as “pleomorphic sarcoma, not otherwise specified.”

It is usually impossible to give a diagnosis of dedifferentiated liposarcoma by FNAB or even percutaneous needle core biopsy. The diagnosis of dedifferentiated liposarcoma depends on the finding of a high-grade “non-liposarcomatous” sarcoma juxtaposed to a well-differentiated liposarcoma. The development of a high-grade non-liposarcomatous sarcoma in the region of a previously excised well-differentiated liposarcoma also justifies the designation of dedifferentiated liposarcoma.⁶³ Not surprisingly, FNAB usually samples only the high-grade component. As with pleomorphic liposarcoma, most appear cytologically malignant, but the morphologic features are relatively nonspecific; therefore, most are diagnosed simply as pleomorphic sarcomas. Excisional biopsy is usually required for recognition as a dedifferentiated liposarcoma. Similar sampling problems are also encountered in other forms of dedifferentiated sarcoma, principally dedifferentiated chondrosarcoma.⁶⁴

Myxofibrosarcoma

Myxofibrosarcoma represents one of the most common soft tissue sarcomas, usually arising within the extremities of elderly patients.⁶⁵ In contrast to other myxoid sarcomas, myxofibrosarcoma frequently arises within dermal or subcutaneous soft tissues. The lesions vary from hypocellular, mostly myxoid, and largely spindle cell features (low-grade) to a hypercellular and pleomorphic cell appearance (high-grade).⁶⁵ The latter has often

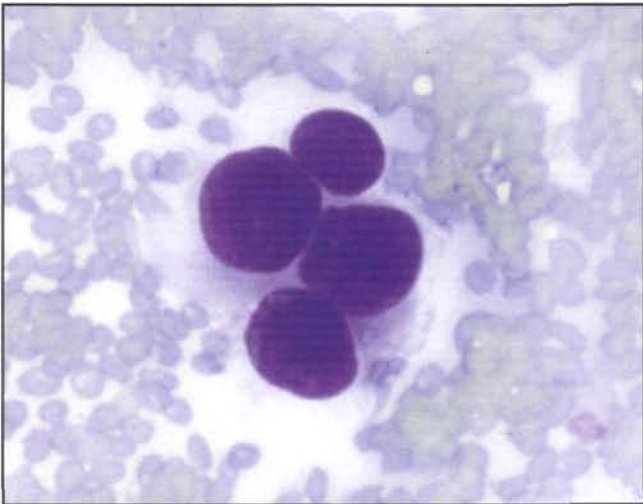


Image 22 Round cell liposarcoma, which is often admixed with myxoid liposarcoma, is characterized by substantially larger, round to ovoid tumor cells with little to no cytoplasm (rapid Romanowsky, $\times 400$).

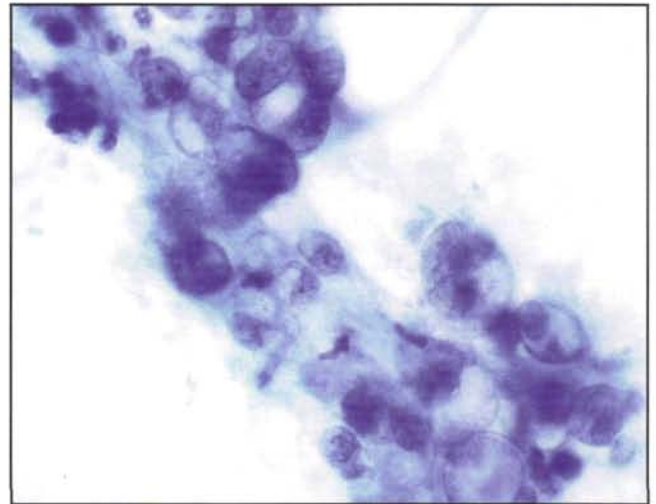


Image 23 Pleomorphic liposarcoma with multivacuolated lipoblasts (Papanicolaou, $\times 400$).

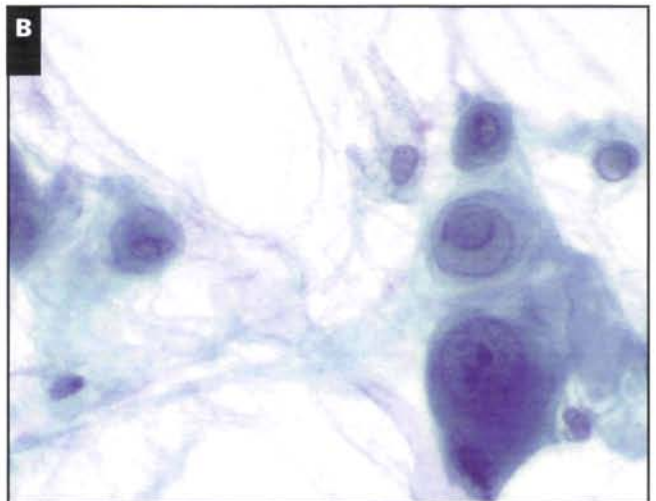
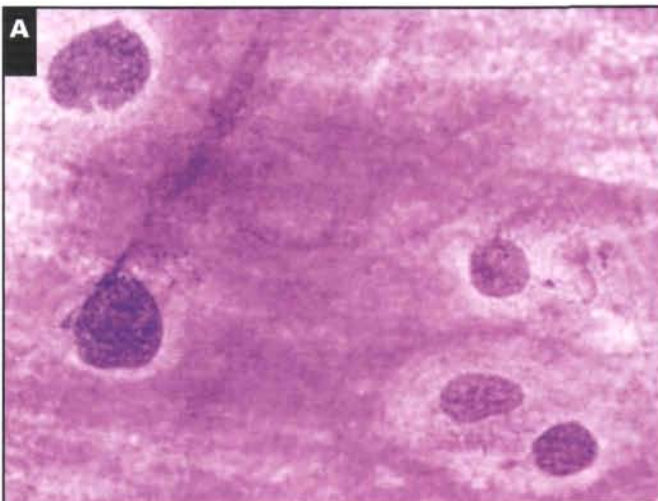


Image 24 Myxofibrosarcoma characterized by a background granular film of myxoid material (usually best visualized on Romanowsky-stained smears) and scattered, mostly single, large ovoid to round tumor cells with scant to vacuolated cytoplasm and substantial nuclear pleomorphism (A, rapid Romanowsky, $\times 400$; B, Papanicolaou, $\times 600$).

been referred to as myxoid MFH. FNAB generally yields slightly to moderately cellular smears within a background granular film of myxoid material. The cells range from round to spindle. The degree of nuclear atypia and cellularity tends to correlate with the grade of the tumor.⁶⁶ Nevertheless, even low-grade examples of myxofibrosarcoma typically show a greater degree of nuclear variability than that seen with myxoid liposarcoma or myxoma

Image 24. Although curvilinear capillarylike blood vessels are frequently observed in histologic sections of myxofibrosarcoma, in our experience, they are less commonly seen in cytologic preparations.⁶⁶

The differential diagnosis of myxofibrosarcoma includes extraskeletal myxoid chondrosarcoma (EMC). Similar to myxoid liposarcoma, most cases of EMC occur in adults, frequently arising in the lower extremities, especially the thigh and popliteal fossa. Cytologically, in addition to a background film of myxoid stroma, EMC also displays cohesive clumps and/or fragments of stroma, some of which may contain cells arranged in lacunae indicative of cartilaginous differentiation.⁶⁷ The individual tumor cells tend to be uniform and round to ovoid and possess hyperchromatic nuclei surrounded by a relatively thin rim of cytoplasm. Cytogenetic analysis may be useful, as the majority of cases

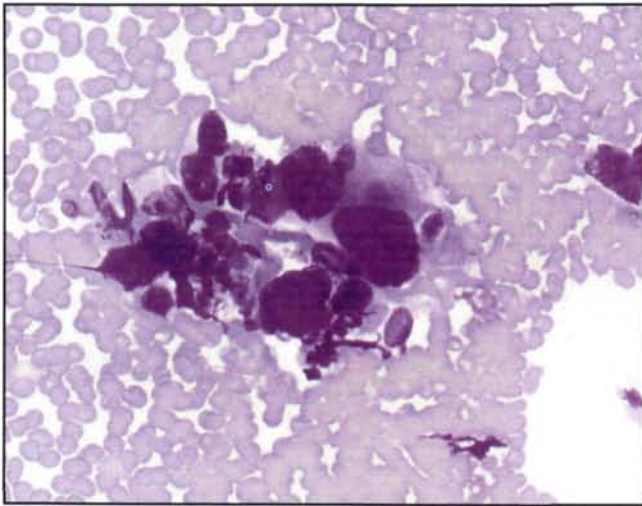


Image 25 Malignant fibrous histiocytoma with a solitary and small cohesive fragment of markedly anaplastic and pleomorphic tumor giant cells. Such findings are nonspecific and may be seen in a variety of pleomorphic sarcomas (rapid Romanowsky, $\times 200$).

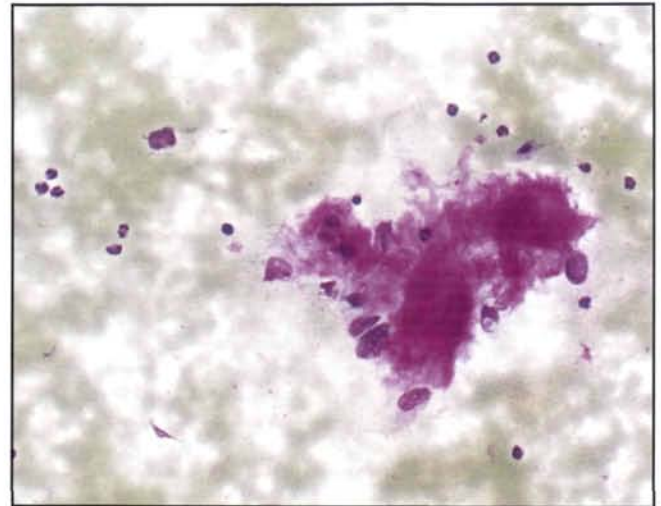


Image 26 Osteosarcoma showing a fragment of magenta-appearing matrix material. As osteoid, bone, chondroid, hyaline cartilage, dense collagen, and even myxoid material may appear tinctorially similar, reliable distinction among these matrices is often difficult (rapid Romanowsky, $\times 200$).

show a nonrandom, reciprocal translocation, $t(9;22)(q22-31;q11-12)$ with the EWS/TEC gene fusion product.⁶⁸

Malignant Fibrous Histiocytoma

The diagnosis of MFH has undergone intense scrutiny during the past decade.^{65,69} Tumors composed of a markedly pleomorphic spindle cell population arranged in fascicles and storiform patterns but lacking other significant features (eg, lipoblasts) were often interpreted as MFH.⁶⁹ Thus, the diagnosis of MFH has increasingly become a diagnosis of exclusion.

In our experience and that of others, most so-called lesions conforming to the rather nonspecific morphologic pattern of MFH can be further classified into other sarcoma subtypes—pleomorphic liposarcoma, dedifferentiated liposarcoma, pleomorphic leiomyosarcoma, and pleomorphic rhabdomyosarcoma—with meticulous sampling and ancillary techniques.⁶⁹ Indeed, in adults with pleomorphic sarcomas, the diagnoses of melanoma and sarcomatoid carcinoma must also be considered. A thorough clinical history and judicious use of ancillary studies (eg, immunocytochemistry) will usually help exclude these entities. Not surprisingly, subtyping a pleomorphic sarcoma is considerably more difficult in small biopsy specimens, such as FNAB. Most cytologic smears are slightly to moderately cellular and composed of mostly solitary neoplastic cells with moderate to marked nuclear pleomorphism. Unfortunately, the cytologic features are not diagnostic, and we

typically render a diagnosis of “pleomorphic sarcomas, not otherwise specified” **Image 25**.⁷⁰ The presence of matrix material (eg, osteoid) is the only specific feature allowing separation of MFH from extraskeletal osteosarcoma. Unfortunately, dense collagen cannot be reliably distinguished from osteoid in most cytologic preparations **Image 26**.⁷⁰ At our institution, adult patients with pleomorphic sarcomas, regardless of histologic subtype are treated similarly, usually with surgical resection followed by adjuvant therapy (eg, radiation, chemotherapy, or both).

Conclusion

FNAB represents a valuable method of establishing a clinically useful definitive diagnosis in most soft tissue sarcomas. Moreover, distinction between benign and malignant tumors is usually possible.³ Clinical and radiologic correlation is absolutely essential for its implementation.⁷¹ By using ancillary techniques, most small round cell and spindle cell sarcomas can be easily subtyped. The usefulness of histologic subtyping of epithelioid/polygonal cell sarcomas by FNAB awaits further investigation and larger series. Separation among the myxoid sarcomas—myxoid liposarcoma, myxofibrosarcoma, and myxoid chondrosarcoma—is usually possible based on cytomorphologic features alone. Nevertheless, some soft tissue sarcomas (eg, well-differentiated liposarcoma, hemangiopericytoma, MC) are probably best diagnosed by percutaneous core needle or incisional biopsy methods. Similarly, distinction among the

pleomorphic sarcomas is not generally possible by FNAB but, at least at our institution, does not alter initial therapy. As the use of FNAB and the availability of ancillary techniques on cell block material becomes more widely accepted, we expect that FNAB may even become "standard" for establishing definitive diagnoses in a large proportion of sarcomas.

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References

- Pollock RE, Karnell LH, Menck HR, et al. The National Cancer data base report on soft tissue sarcoma. *Cancer*. 1996;78:2247-2257.
- Fletcher CDM, Young AE. Fine needle aspiration cytology of soft tissue tumors. *Br J Surg*. 1987;74:965. Letter.
- Layfield LJ, Anders KH, Glasgow BJ, et al. Fine needle aspiration of primary soft tissue lesions. *Arch Pathol Lab Med*. 1986;110:420-424.
- DeMay RM. Soft-tissue tumors. In: *The Art & Science of Cytopathology: Aspiration Cytology*. Chicago, Ill: ASCP Press; 1996:559-642.
- Silverman JF, Geisinger KR. Retroperitoneum and pelvis. In: *Fine Needle Aspiration Cytology of the Thorax and Abdomen*. New York, NY: Churchill Livingstone; 1996:219-258.
- Kilpatrick SE, Teot LA, Geisinger KR, et al. Relationship of DNA ploidy to histology and prognosis in rhabdomyosarcoma: comparison of flow cytometry and image analysis. *Cancer*. 1994;74:3227-3233.
- Leuschner I, Radig K, Harms D. Desmoplastic small round cell tumor. *Semin Diagn Pathol*. 1996;13:204-212.
- Schlott T, Nagel H, Ruschenburg I, et al. Reverse transcriptase polymerase chain reaction for detecting Ewing's sarcoma in archival fine needle aspiration biopsies. *Acta Cytol*. 1997;41:795-801.
- Coffin CM. The new International Rhabdomyosarcoma Classification, its progenitors, and considerations beyond morphology. *Adv Anat Pathol*. 1997;4:1-16.
- Geisinger KR, Silverman JF, Wakely PW. Soft tissue. In: *Pediatric Cytopathology*, Chicago, Ill: ASCP Press; 1994:259-281.
- Ahktar M, Ali MA, Bakry M, et al. Fine needle aspiration biopsy diagnosis of rhabdomyosarcoma: cytology, histologic, and ultrastructural correlations. *Diagn Cytopathol*. 1992;8:465-474.
- Dehner LP. Primitive neuroectodermal tumor and Ewing's sarcoma. *Am J Surg Pathol*. 1993;17:1-13.
- Renshaw AA, Perez-Atayde AR, Fletcher JA, et al. Cytology of typical and atypical Ewing's sarcoma/PNET. *Am J Clin Pathol*. 1996;106:620-624.
- Stevenson AJ, Chatten J, Bertoni F, et al. CD99 (p30/32 MIC2) neuroectodermal/Ewing's sarcoma antigen as an immunohistochemical marker: review of more than 600 tumors and the literature experience. *Appl Immunohistochemistry*. 1994;2:231-240.
- Jeon IS, Davis JN, Braun BS, et al. A variant Ewing's sarcoma translocation (7;22) fuses the EWS gene to the ETS gene ETV1. *Oncogene*. 1995;10:1229-1234.
- Sorenson PH, Lessnick SL, Lopez-Terrada D, et al. A second Ewing's sarcoma translocation, t(21;22), fuses the EWS gene to another ETS-family transcription factor, ERG. *Nat Genet*. 1994;6:146-151.
- Thorne P, Squire J, Chilton-Macneill S, et al. Is the EWS/FLI-1 fusion transcript specific for Ewing sarcoma and peripheral primitive neuroectodermal tumor? a report of four cases showing this transcript in a wider range of tumor types. *Am J Pathol*. 1996;148:1125-1138.
- Sorenson PH, Tiraboseo R, Xian XF, et al. Molecular studies of non-embryonal rhabdomyosarcoma: evidence for genetic heterogeneity. *Lab Invest*. 1995;72:145A. Abstract.
- DeLorimier AA, Bragg KU, Linden G. Neuroblastoma in childhood. *Am J Dis Child*. 1969;118:441-450.
- Enzinger FM, Weiss SW. Primitive neuroectodermal tumors and related lesions. In: *Soft Tissue Tumors*. 3rd ed. St Louis, Mo: Mosby; 1995:929-944.
- Kreiter SR, Geisinger KR, Chauvenet AR, et al. DNA ploidy analysis in neuroblastoma: flow cytometry versus image analysis [abstract]. *Acta Cytol*. 1992;36:629.
- Silverman JF, Dabbs DJ, Ganick DJ, et al. Fine needle aspiration cytology of neuroblastoma, including peripheral neuroectodermal tumor, with immunocytochemical and ultrastructural confirmation. *Acta Cytol*. 1988;32:367-376.
- Nakashima Y, Unni KK, Shives TC, et al. Mesenchymal chondrosarcoma of bone and soft tissue: a review of 111 cases. *Cancer*. 1986;57:2444-2453.
- Walaas L, Kindblom L-G, Gunterberg B, et al. Light and electron microscopic examination of fine needle aspirates in the preoperative diagnosis of cartilaginous tumors. *Diagn Cytopathol*. 1990;6:396-408.
- Granter SR, Renshaw AA, Fletcher CD, et al. CD99 reactivity in mesenchymal chondrosarcoma. *Hum Pathol*. 1996;27:1273-1276.
- Kilpatrick SE, Teot LA, Stanley MW, et al. Fine needle aspiration biopsy of synovial sarcoma: a cytomorphologic analysis of primary, recurrent, and metastatic tumors. *Am J Clin Pathol*. 1996;106:769-775.
- Akerman M, Willen H, Carlen B, et al. Fine needle aspiration (FNA) of synovial sarcoma: a comparative histological-cytological study of 15 cases, including immunohistochemical, electron microscopic and cytogenetic examination and DNA-ploidy analysis. *Cytopathology*. 1996;7:187-200.
- Dei Tos AP, Wadden C, Calonje E, et al. Immunohistochemical demonstration of glycoprotein p30/32 MIC2 (CD99) in synovial sarcoma: a potential cause of diagnostic confusion. *Appl Immunohistochemistry*. 1995;3:168-173.
- Fletcher JA. Cytogenetics and molecular biology of soft tissue tumors. In: Weiss SW, Brooks JSJ, eds. *Soft Tissue Tumors*. Monographs in Pathology; No. 38. Philadelphia, Pa: William & Wilkins, 1996:37-64.

30. Pritchard DJ, Soule EH, Taylor WF, et al. Fibrosarcoma: a clinicopathologic and statistical study of 199 tumors of the soft tissues of the extremities and trunk. *Cancer*. 1974;33:888–897.
31. Enzinger FM, Weiss SE. Fibrosarcoma. In: *Soft Tissue Tumors*. 3rd ed. St Louis, Mo: Mosby; 1995:269–291.
32. Stout AP. The malignant tumors of the peripheral nerves. *Am J Cancer*. 1935;25:1–36.
33. Ducatman BS, Scheithauer BW, Piepgras DG. Malignant peripheral nerve sheath tumors: a clinicopathologic study of 120 cases. *Cancer*. 1986;57:2006–2021.
34. McGee RS Jr, Ward WG, Kilpatrick SE. Malignant peripheral nerve sheath tumor: a fine needle aspiration biopsy study. *Diagn Cytopathol*. 1997;17:298–305.
35. Resnick JM, Fanning CV, Caraway NP, et al. Percutaneous needle biopsy diagnosis of benign neurogenic neoplasms. *Diagn Cytopathol*. 1997;16:17–25.
36. Johnson TL, Lee MW, Meis JW, et al. Immunohistochemical characterization of malignant peripheral nerve sheath tumors. *Surg Pathol*. 1991;4:121–135.
37. Weiss SW, Langloss JM, Enzinger FM. Value of S-100 protein in the diagnosis of soft tissue tumors with particular reference to benign and malignant Schwann cell tumors. *Lab Invest*. 1983;49:299–308.
38. Fisher C, Scholfield JB. S-100 protein positive synovial sarcoma. *Histopathology*. 1991;19:375–377.
39. Mentzel T, Calonje E, Nascimento AG, et al. Infantile hemangiopericytoma versus infantile myofibromatosis: a study of a series suggesting a continuous spectrum of infantile myofibroblastic lesions. *Am J Surg Pathol*. 1994;18:922–930.
40. Enzinger FM, Smith BH. Hemangiopericytoma: an analysis of 106 cases. *Hum Pathol*. 1976;7:61–81.
41. Geisinger KR, Silverman JF, Cappelari JO, et al. Fine needle aspiration cytology of malignant hemangiopericytomas with ultrastructural and flow cytometric analyses. *Arch Pathol Lab Med*. 1990;114:705–710.
42. Porter PL, Bigler SA, McNutt M, et al. The immunophenotype of hemangiopericytomas and glomus tumors, with special reference to muscle protein expression: an immunohistochemical study and review of the literature. *Mod Pathol*. 1990;136:771–786.
43. Lucas DR, Nascimento AG, Sim FH. Clear cell sarcoma of soft tissues: Mayo Clinic experience with 35 cases. *Am J Surg Pathol*. 1992;16:1197–1204.
44. Almeida MM, Nunes AM, Frable WJ. Malignant melanoma of soft tissue. a report of three cases with diagnosis by fine needle aspiration cytology. *Acta Cytol*. 1994;38:241–246.
45. Tao L-C, Davidson DD. Aspiration biopsy cytology of smooth muscle tumors: a cytologic approach to the differentiation between leiomyosarcoma and leiomyoma. *Acta Cytol*. 1993;37:300–308.
46. Kilpatrick SE, Mentzel T, Fletcher CDM. Leiomyoma of deep soft tissue: clinicopathologic analysis of a series. *Am J Surg Pathol*. 1994;18:576–582.
47. Lieberman PH, Brennan MF, Kimmel M, et al. Alveolar soft part sarcoma: a clinico-pathologic study of half a century. *Cancer*. 1989;63:1–13.
48. Shabb N, Sneige N, Fanning CV, et al. Fine needle aspiration cytology of alveolar soft part sarcoma. *Diagn Cytopathol*. 1991;63:1–13.
49. Chase DR, Enzinger FM. Epithelioid sarcoma: diagnosis, prognostic indicators, and treatment. *Am J Surg Pathol*. 1985;9:241–263.
50. Pohar-Marinek Z, Zidar A. Epithelioid sarcoma in FNAB smears. *Diagn Cytopathol*. 1994;11:367–372.
51. Guillon L, Wadden C, Coindre J-M, et al. “Proximal-type” epithelioid sarcoma: a distinctive aggressive neoplasm showing rhabdoid features: clinicopathologic, immunohistochemical, and ultrastructural study of a series. *Am J Surg Pathol*. 1997;21:130–146.
52. Arber DA, Kandalaf PL, Mehta P, et al. Vimentin-negative epithelioid sarcoma: the value of an immunohistochemical panel that includes CD34. *Am J Surg Pathol*. 1993;17:302–307.
53. Kleer CG, Unni KK, McLeod RA. Epithelioid hemangioendothelioma of bone. *Am J Surg Pathol*. 1996;20:1301–1311.
54. Nora FE, Scheithauer BW. Primary epithelioid hemangioendothelioma of the brain. *Am J Surg Pathol*. 1996;20:707–714.
55. Mentzel T, Beham A, Calonje E, et al. Epithelioid hemangioendothelioma of skin and soft tissues: a clinicopathologic and immunohistochemical study of 30 cases. *Am J Surg Pathol*. 1997;21:363–374.
56. Kilpatrick SE, Kopyay PD, Ward WG, et al. Epithelioid hemangioendothelioma of bone and soft tissue: a fine needle aspiration biopsy study with histologic and immunohistochemical confirmation. *Diagn Cytopathol*. In press.
57. Pettinato G, Insaboto L, DeChiara A, et al. Epithelioid hemangioendothelioma of soft tissue: fine needle aspiration cytology, histology, electron microscopy and immunohistochemistry of a case. *Acta Cytol*. 1986;30:194–220.
58. Walaas L, Kindblom L-G. Lipomatous tumors: a correlative cytologic and histologic study of 27 tumors examined by fine needle aspiration cytology. *Hum Pathol*. 1985;16:6–18.
59. Fletcher CDM, Akerman M, Dal Cin P, et al. Correlation between clinicopathologic features and karyotype in lipomatous tumors: a report of 178 cases from the chromosomes and morphology (CHAMP) collaborative study group. *Am J Pathol*. 1996;148:623–630.
60. Kilpatrick SE, Doyon J, Choong PFM, et al. The clinicopathologic spectrum of myxoid and round cell liposarcoma: a study of 95 cases. *Cancer*. 1996;77:1450–1458.
61. Tallini G, Akerman M, Dal Cin P, et al. Combined morphologic and karyotypic study of 28 myxoid liposarcomas: implications for a revised morphologic typing. *Am J Surg Pathol*. 1996;20:1047–1055.
62. Szadowska A, Lasota J. Fine needle aspiration cytology of myxoid liposarcoma: a study of 18 tumors. *Cytopathology*. 1993;4:99–106.
63. Henricks WH, Chu YC, Goldblum JR, et al. Dedifferentiated liposarcoma: a clinicopathologic analysis of 155 cases with a proposal for an expanded definition of dedifferentiation. *Am J Surg Pathol*. 1997;21:271–281.
64. Kilpatrick SE, Pike EJ, Ward WG, et al. Dedifferentiated chondrosarcoma in patients with multiple osteochondromatosis: report of a case and a review of the literature. *Skeletal Radiol*. 1997;26:370–374.
65. Mentzel T, Calonje E, Wadden C, et al. Myxofibrosarcoma: clinicopathologic analysis of 75 cases with emphasis on the low-grade variant. *Am J Surg Pathol*. 1996;20:391–405.

66. Kilpatrick SE, Ward WG. Myxofibrosarcoma of soft tissues: a cytomorphologic analysis of a series. *Diagn Cytopathol*. In press.
67. Wakely PE, Geisinger KR, Cappellari JO, et al. Fine-needle aspiration cytopathology of soft tissue: chondromyxoid and myxoid lesions. *Diagn Cytopathol*. 1995;12:101–105.
68. Kilpatrick SE, Inwards CY, Fletcher CDM, et al. Myxoid chondrosarcoma (chordoid sarcoma) of bone: a report of two cases and review of the literature. *Cancer*. 1997;79:1903–1910.
69. Fletcher CDM. Pleomorphic malignant fibrous histiocytoma: fact or fiction? a critical appraisal based on 159 tumors diagnosed as pleomorphic sarcoma. *Am J Surg Pathol*. 1992;16:213–228.
70. Kilpatrick SE, Pike EJ, Geisinger KR, et al. Chondroblastoma of bone: use of fine-needle aspiration biopsy and potential diagnostic pitfalls. *Diagn Cytopathol*. 1997;16:65–71.
71. Kilpatrick SE, Ward WG, Savage PD. Fine needle aspiration biopsy of mesenchymal lesions: the value of clinicoradiologic correlation and the importance of histogenetic subtyping. *Am J Clin Pathol*. 1997;108:237. Letter.