The cytology of soft tissue tumours

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Fine needle aspiration (FNA) and cytodiagnosis is an alternative to open or coarse needle biopsy in the primary diagnosis of soft tissue tumours.

There are a number of advantages with FNA:

- hospitalization is not necessary,
- minimal risk for complications such as bleeding or infection,
- negligible risk of tumour spread,
- compared to open or coarse needle biopsy it is easy to collect material from different parts of large tumours,
- a preliminary report is possible within 15–20 minutes after the needling, and
- information relating to further work-up of the lesion (further investigations or suggested therapy) is possible to convey to the patient at the first visit.

The present use of fine needle aspiration (FNA) and cytodiagnosis as the primary and often definitive diagnosis before treatment of soft tissue tumours is based on the following prerequisites:

1. The treatment for the majority of soft tissue tumours, benign as well as sarcomas is surgery. For the planning of the surgery the knowledge of histotype is of less importance for the orthopedic surgeon than the size and site of the tumour and its relationship to vessel-and nerve bundles and bone.

2. The important task for the cytopathologist is thus to diagnose reliably the mass as a soft tissue tumour, benign or malignant, and to exclude other tumour types as carcinoma metastases, malignant melanoma and malignant lymphoma. It is, of course, useful if it is possible to define the malignancy grade of sarcomas and to suggest a specific histotype.

3. The planning of the treatment is based on the combined evaluation of clinical and radiographic data and the cytodiagnosis. This approach is comparable to that commonly used for breast lesions (palpation, mammography and cytodiagnosis); when there is a discrepancy between the results of the different methods, a re-evaluation of data must be considered as well as to supplement the FNA with a surgical biopsy.

When the surgery involves amputation or complex procedures, and when preoperative treatment is considered the cytodiagnosis must be as reliable as a histopathologic diagnosis of a biopsy specimen with regard to histotype as well as malignancy grade and surgical biopsy sometimes must be performed.

4. A close cooperation between the orthopedic surgeon and the cytopathologist is mandatory and ideally patients should be referred with virgin tumours to a center where the surgeon and cytopathologist often together decide the insertation point of the needle. Optimal diagnostic results are reached when it is the same person who performs the FNA and examines the smears.

Technique

The FNA of soft tissue tumours/lesions is generally performed in the same way as for other targets. It is advisable to use needles with a stylet for deep-seated masses. The stylet prevents normal or reactively changed tissue around the tumour from beeing part of the smears.

It is also advantageous to make wet-fixed as well as air-dried smears. In wet-fixed material stained with hematoxylin-eosin (HE) or Papanicolaou (Pap) the nuclear details such as membranes, chromatin structure and nucleoli are very well visualized while air-dried May-Grünwald-Giemsa (MGG) stained aspirates are superior for the evaluation of cytoplasmic details, myxoid background matrix and chondroid fragments.

The aspirations are as a rule performed from the vertex of the tumour provided that the orthopedic surgeon does not suggest another site. All passes with the needle are performed from the same insertation point in the skin. Whith each pass the needle is directed into different parts of the tumour. The insertation point is tatooed at in order to make it easy to remove the needle track at the operation.

Malignancy grading of soft tissue sarcoma is possible in low grade and high grade malignant sarcomas, respectively. The main parameters used are cellular and nuclear pleomorphism, chromatin structure, nucleolar size and shape, mitotic frequency, atypical mitoses and the presence of necrosis.

When the yield is rich with preserved cells soft tissue tumour aspirates are suitable for ancillary diagnostic methods such as immunocytochemistry, electron microscopic examination, DNA ploidy and chro-

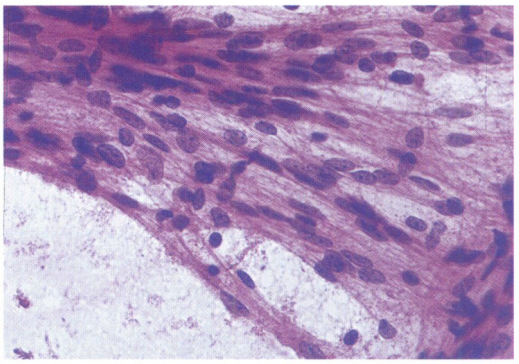

Figure 1. A. ***Neurilemoma.*** *Cohesive tumour tissue fragment with spindle-shaped palisading nuclei in a fibrillar background. HE, ×100.*

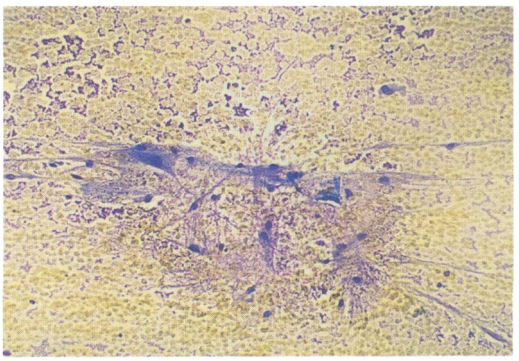

Figure 1. B. ***Intramuscular myxoma.*** *Loosely attached spindle cells with long cytoplasmic processes in an abundant myxoid background substance. MGG, ×25.*

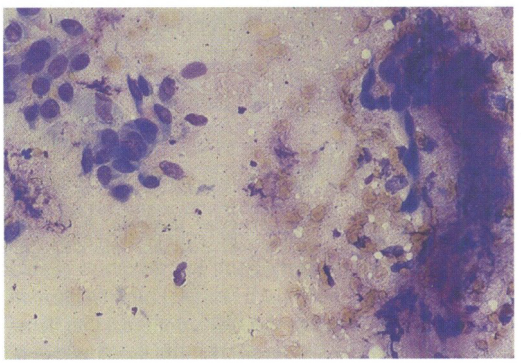

Figure 1. C. ***Desmoid.*** *The two important criteria for diagnosis: a cluster of fibroblasts and a fragment of collagenous intercellular substance (arrow). MGG, ×160.*

mosomal analysis. When the material for smearing has been taken care of, the needle and syringe are rinsed with suitable medium after each pass with the needle and a further one or two aspirates are entirely used for the supplementary diagnostics.

Benign soft tissue tumours/lesions

The benign pseudosarcomatous soft tissue lesions have been extensively studied in FNA and with our present knowledge a reliable diagnosis is the rule in the typical case (Dahl and Åkerman 1981, Rööser et al. 1989, Lundgren et al. 1992).

Of the 5 most common benign soft tissue tumours, lipoma, neurilemoma, intramuscular myxoma, desmoid and hemangioma, diagnostic criteria have been defined, except for hemangioma (Walaas and Kindblom 1985, Åkerman and Rydholm 1987, Dahl et al. 1984, Ryd et al. 1986, Åkerman and Rydholm 1983, Åkerman 1995) (Figure 1). Hemangioma, however, is not suitable for FNA, the suggestion of a diagnosis of hemangioma most often is based on the combination of clinical and radiographic data and aspiration of blood under pressure.

Sarcoma

In the majority of the soft tissue sarcomas, diagnostic criteria for the diagnosis of specific histotypes have not been described, however, it is in most instances possible to diagnose the tumour as benign or as a sarcoma.

In order to faciliate a reliable diagnosis of sarcoma, sarcoma aspirates may be classified into different categories based on the predominant pattern, although there is a certain overlap between these patterns such a classification is useful in the diagnostic work up for a suggestion of type as well as for the recognition of the important diagnostic pitfalls.

The majority of the soft tissue sarcomas belong to one of the following patterns.

Pleomorphic pattern

The typical features are a marked variation in cellular size and shape and nuclear pleomorphism. Nucleoli are often large and prominent and multinucleated tumour cells are always observed. The cells are either dispersed or arranged in sheets or clusters. Typical examples are pleomorphic liposarcoma and leiomyosarcoma and the pleomorphic sarcomas diagnosed as storiform-pleomorphic MFH. Less common are extraskeletal osteosarcoma and pleomorphic malignant peripheral nerve sheath tumours (MPNST) (Figure 2).

Important diagnostic pitfalls are nodular fascitis and proliferative myositis and fasciitis, pleomorphic malignant melanoma, anaplastic carcinoma and anaplastic large cell lymphoma.

Spindle cell pattern

The predominant features are more or less atypical spindle cells arranged in fascicles or sheets mixed with dispersed cells. The spindle cells often are elon-

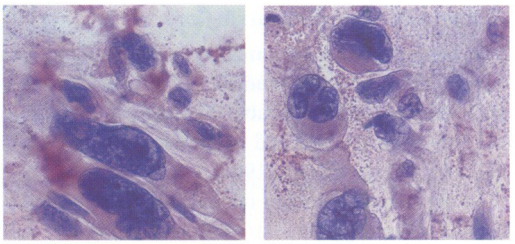

Figure 2. A. ***Pleomorphic sarcoma****, histologic diagnosis storiform/pleomorphic MFH. HE, ×200.*

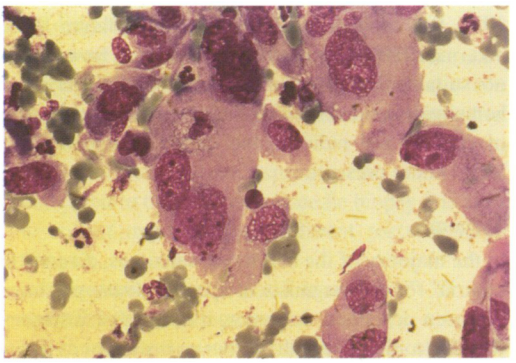

Figure 2. B. Pleomorphic sarcoma, histologic diagnosis pleomorphic leiomyosarcoma. MGG ×125.

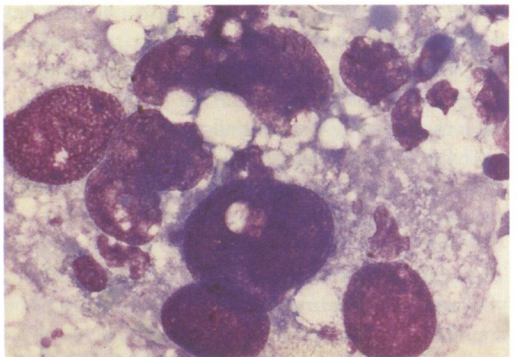

Figure 2. C. Pleomorphic sarcoma, histologic diagnosis pleomorphic liposarcoma. In this field highly atypical multivacuolated lipoblasts. Type diagnosis is possible in this smear. MGG, ×200.

macroscopic appearance of the aspirate: more or less abundant, often slightly haemorrhagic thick and viscious fluid. At the microscopic low power view this myxoid matrix gives the smear a blue or blue-violett background staining in the MGG stained material. In this background there are a mixture of dispersed cells or cellgroups. The cellular pattern is variable, spindly, round cell or pleomorphic. The most common sarcomas in this group are myxoid liposarcoma and myxofibrosarcoma and less commonly extraskeletal myx-

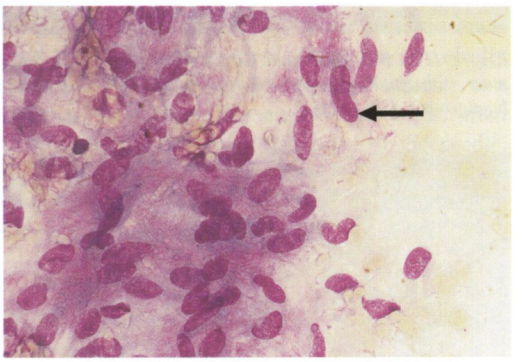

Figure 3. A. ***Leiomyosarcoma.*** *The blunt-ended nuclei strongly favor a leiomyosarcoma diagnosis in this smear. MGG, ×125.*

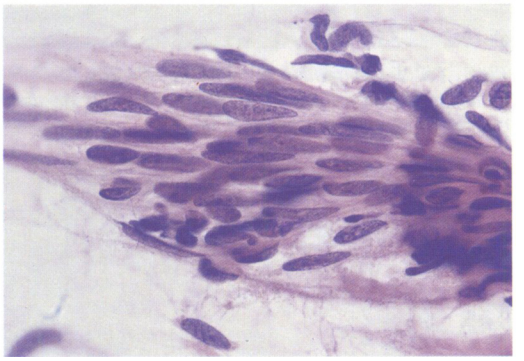

Figure 3. B. ***Monophasic synovial sarcoma.*** *A cytologi diagnosis of spindle cell sarcoma is reliable but a specific type diagnosis difficult. HE, ×250.*

gated with uni-or bipolar cytoplasm with fusiform or ovoid nuclei. Scattered large rounded, polygonal or triangular cells are often also present (leiomyosarcoma). The majority of leiomyosarcomas belong to this category as MPNST as well as the rare fibrosarcoma and pure monophasic synovial sarcoma (Figure 3). The clinicaly most important differential diagnoses are neurilemoma and desmoid.

Myxoid pattern

A common feature in this group of sarcomas is the oid chondrosarcoma (Figure 4). Soft tissue tumours/lesions which may be misinterpreted as myxoid sarcoma are above all intramuscular myxoma, nodular fasciitis and neurilemoma with myxoid areas. A rare diagnostic pitfall is myxoid malignant melanoma.

Small round-ovoid cell pattern

The typical smear is cellular and composed of small to medium sized cells with rounded or ovoid nuclei and a variable amount of cytoplasm. The cellular shape is rounded, fusiform or ovoid. There are no spe-

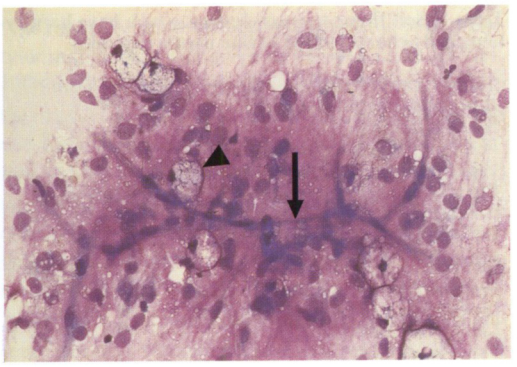

Figure 4. A. ***Myxoid liposarcoma.*** *The three important features for a cytodiagnosis of myxoid liposarcoma are present in this field; myxoid back ground matrix, a branching capillary network (arrow) and lipoblasts (arrowhead). MGG, ×75.*

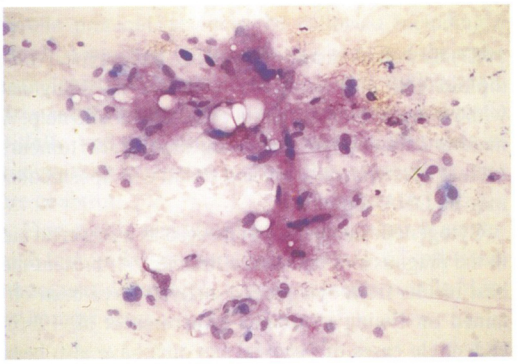

Figure 4. B. Low grade malignant ***myxofibrosarcoma.*** *Moderately atypical, predominantly spindle shaped cells in a myxoid back ground matrix. The vacuoles are in the background and not in lipoblasts. MGG, ×50.*

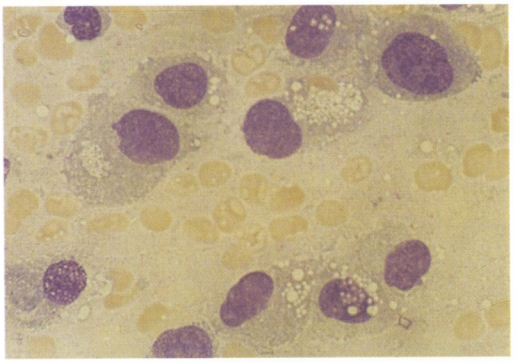

Figure 5. A. ***Round cell liposarcoma.*** *Dispersed lipoblasts with multivacuolated cytoplasm. MGG, ×250.*

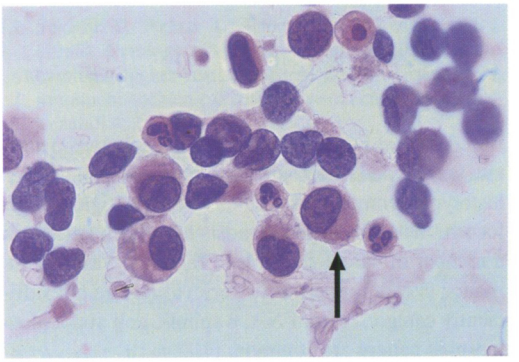

Figure 5. B. ***Alveolar rhabdomyosarcoma.*** *A mixture of stripped nuclei and preserved myoblast-like cells (arrow): eccentric nuclei and strongly eosinophilic cytoplasm. HE, ×250.*

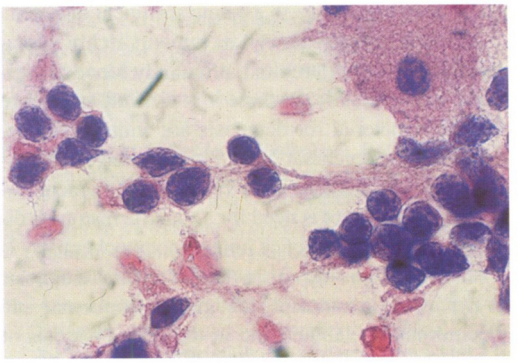

Figure 5. C. ***Neuroblastoma.*** *Small cells with irregular hyperchromatic nuclei, loosely attached to each other by thin, fibrillar cytoplasmic extensions. HE, ×250.*

cific nuclear features. The predominant sarcomas exhibiting this pattern are the majority of synovial sarcomas, pure round cell liposarcoma, hemangiopericytoma, extraskeletal Ewing's sarcoma and other peripheral primitive neuroectodermal tumours, alveolar rhabdomyosarcoma, embryonal rhabdomyosarcoma chiefly composed of undifferentiated round cells and neuroblastoma (Figure 5). When the yield is rich small cell carcinoma and non-Hodgkin lymphoma are the main diagnostic pitfalls.

In some of the sarcomas in this group (Ewing's sarcoma, rhabdomyosarcoma, neuroblastoma) a specific type diagnosis is necessary as the treatment often is a combination of preoperative chemotherapy and surgery.

Epithelioid cell pattern

Three rare sarcomas belong to this category: epithelioid cell sarcoma, clear cell sarcoma and alveolar soft part sarcoma. The tumour cell is epithelial-like, rounded or polygonal often with well demarcated cytoplasmic borders and rounded, ovoid or irregular nuclei. Nucleoli are often prominent (Figure 6). In the differential diagnosis carcinoma, malignant melanoma and granular cell tumour are the most important.

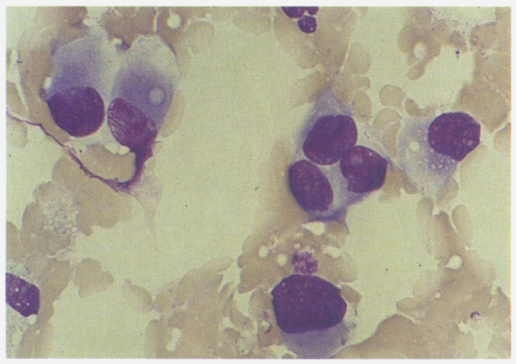

Figure 6. ***Clear cell sarcoma.*** *Epithelial like cells with sharp cytoplasmic borders and irregular, hyperchromatic nuclei. MGG, ×250.*

Table 1. Soft tissue tumours/lesions which have been cytologically characterized in fine needle aspirates

Benign tumours/lesions	
Nodular fasciitis	(6)
Proliferative fasciitis and myositis	(7)
Pseudomalignant myositis ossificans	(11)
Lipoma	(16, 20)
Neurilemoma	(5, 10)
Intramuscular myxoma	(21)
Sarcoma	
Malignant fibrous histiocytoma	(8, 15)
Liposarcoma	(16, 20)
Leiomyosarcoma	(4)
Synovial sarcoma	(23)
Rhabdomyosarcoma	(1, 12, 13)
Neuroblastoma	(2)
Alveolar soft part sarcoma	(9, 14)
Clear cell sarcoma	(3)

Figures in parentheses refer to the reference list.

Accuracy of FNA in the diagnosis of soft tissue tumours

Based on thorough comparative studies between aspirate smears and histologic material from well defined histotypes, common as well as rare, cytologic criteria for a reliable histotype diagnosis have been defined in a number of sarcoma entities (Table 1). Vascular tumours, except for hemangiopericytoma, are not sufficiently categorized in FNA, a spindle cell and a pleomorphic pattern are common.

In the majority of tumours the FNA yield is sufficient for microscopic evaluation and diagnosis. In tumours with an abundant collagenous intercellular substance or when the stroma is hyalinized it might be difficult or impossible to aspirate sufficient material.

Vascular tumours as well as tumours richly vascularized are another problem; often only blood is aspirated. Other situations where it is difffiult to achieve sufficient material for diagnosis are wide spread necrosis, cystic degeneration and haemorrhage.

Adjunctive methods are a valuable supplement, especially when there is need for a specific histotype diagnosis. In our experience immmunocytochemistry is a valuable diagnostic aid in the differential diagnosis of carcinoma metastases, malignant lymphoma and pleomorphic melanoma and in the type diagnosis of the small malignant round cell tumours as rhabdomyosarcoma, extraskeletal Ewing's sarcoma and neuroblastoma as well as to differentiate between smoth muscle and peripheral nerve sheath tumours.

We have found electron microscopic examination especially useful in the diagnosis of neuroblastoma, atypical extraskeletal Ewing's sarcoma and synovial sarcoma. With regard to DNA-ploidy analysis, aspirates are suitable for flow cytometric (Åkerman et al. 1987) as well as image analysis; an unequivocal non-diploid cell population we consider as malignant while a diploid histogram is of no diagnostic help. A number of sarcomas, including high grade tumours such as synovial sarcoma and round cell liposarcoma may be DNA-diploid.

Cytogenetic analysis has emerged as a powerful aid in the diagnosis of soft tissue tumours. At present the best results from cytogenetic analysis have been obtained on Ewing's sarcoma (Åkerman et al. 1996), and single cases of synovial sarcoma have also been succesfully karyotyped.

In a retrospective study on the efficacy of FNA to correctly diagnose soft tissue tumours as benign or malignant, we re-examined a 20-year material (1972–1991) from our Musculoskeletal Tumor Centre, University Hospital, Lund (Åkerman and Rydholm 1993). Only cases where the primary surgery and the histopathologic examination had been performed in Lund were selected. All aspirations had been performed by cytopathologists at our Department, During the time period 11 cytopathologists had performed the aspirations and together 517 cases were re-evaluated, 315 benign tumours and 202 sarcomas.

The primary diagnoses were classified as follows:

- benign,
- malignant,
- non-diagnostic; (insufficient or inconclusive—not possible to decide wether benign or malignant).

Of the 315 benign tumours 24 (7%) were insufficient, 14 (4%) falsely interpreted as malignant, 10 (3%) inconclusive and 271 (86%) correctly diagnosed as benign. Of the sarcomas the corresponding figures were: insufficient 5 (2%), falsely benign 14 (7%), inconclusive 3 (2%) and a correct malignant diagnosis rendered in 180 (89%).

In the entire material a correct diagnosis of benignity or malignancy was given in 447/475 cases, (94%).

Of the 28 falsely diagnosed tumours 17 belonged to the *spindle cell group* and the next common pitfall was lipomatous tumours. One cause of misinterpretation was when the aspirator failed to hit the lesion and the smears only contained adipose tissue with reactive changes from the area around the tumour and this adipose tissue was either diagnosed as a liposarcoma or as a lipoma.

The cytologic malignancy grade (high/low) was assessed in 127 sarcomas and was correct in 103 and inconclusive in 24.

Summary

In order to achieve the best possible results of FNA certain prerequisites must be followed including a close cooperation between the surgeon and the cytopathologist, the combination of clinical, radiographic data and cytodiagnosis, awareness of the diagnostic pitfalls, and refraining from a specific diagnosis of benignity or malignancy when the cytologic criteria are doubtful.

Fine needle aspiration and cytodiagnosis is a valuable tool in the preoperative diagnosis of soft tissue tumours and may replace open or coarse needle biopsy in most cases.

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