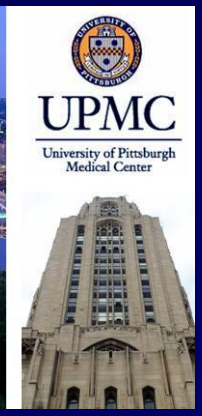
"Cytopathology of Soft Tissue and Bone Lesions:

3rd KAMC CYTOPATHOLOGY SYMPOSIUM

JANUARY 23-25, 2011; MARRIOTT HOTEL, RIYADH, SAUDI ARABIA



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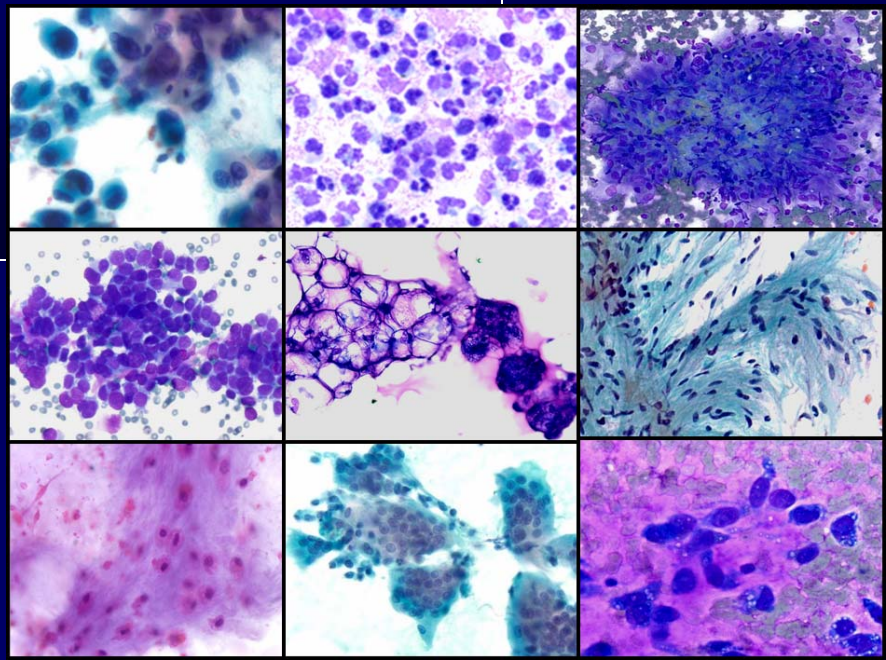
Outlines

- The advantage & Limitations
- Accuracy of FNA
- Practical approach
- Illustrations
- Conclusions



Soft Tissue and Bone Lesions

- a wide variety of lesions with overlapping morphological appearance but with different biologic behavior.
- **The KEY**: Integration of clinical/radiological findings with cytological findings.
- A practical cytomorphological approach for interpretation of FNAC of soft tissue lesions is to **categorize** the lesions based on the background of the smears and the predominance of cell type in the specimen.

Case 1

64/F came to the ER with deterioration for her conscience. She has Hx of breast cancer and found to have a 2-cm occipital mass

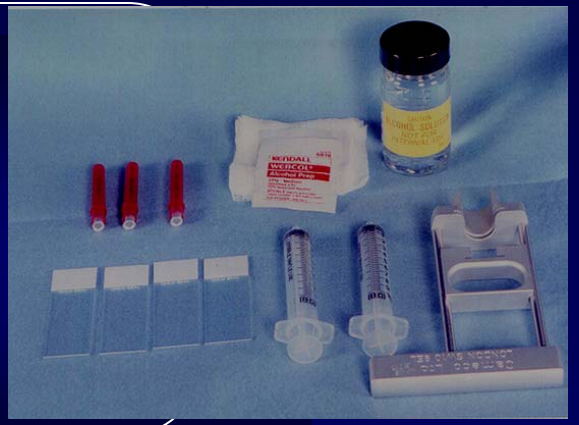
Case 2

11/M came to FNA Clinic for left palm mass that growing slowly.

Soft Tissue & Bone FNA: the advantages

FNA of palpable lesions	$200
Image-Guided FNA	$1,000
Open Biopsy	$6,200

- **Simple, outpatient procedure**
  - Well-tolerated by patients
  - A minimal risk of complications
- **Providing an instant diagnosis**



Khalbuss et al., 20102

Soft Tissue & Bone FNA: the limitations

- Lack of experience of most cytologists
- Greater than 130 different soft tissue lesions
- 99% benign, 1% malignant.
- More than 30 type of sarcoma
- Sarcoma is 1% of all malignant neoplasm
- 9530 malignant cases in 2006 in the USA

(Breast 214K, Lung 174K)

154 lb., Neurofibroma

Practical Approach

1

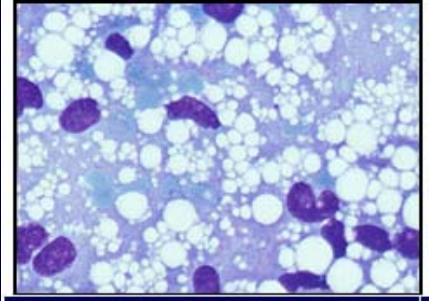
- Inflammatory Lesions
- Spindle cell Lesions
- Lipomatous tumors
- Round/Polygonal Cell Lesions
- Pleomorphic Lesions
- Myxoid Lesions
- Chondroid/Osteoid Lesions
- Giant Cells Lesions

2

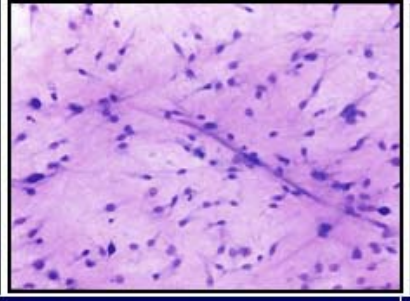
Smart Reporting of FNAB Diagnoses: Be Conservative (Similar to FS)

Lesion → Neoplasm → Malignant

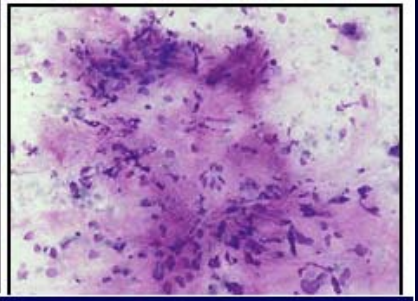
Reactive, Benign, Indeterminate, or Malignant	Neoplastic: Benign, Indeterminate, or Malignant	Malignant, ? type of malignancy
Examples: • Inflammatory lesion • Spindle cell lesion • Giant cell lesion	**Examples:** • Spindle cell neoplasm • Neurogenic tumor • Giant cell tumor	**Examples:** • Sarcoma, • Lymphoma, • Met carcinoma • Angiosarcoma • Rhabdomyosarcoma



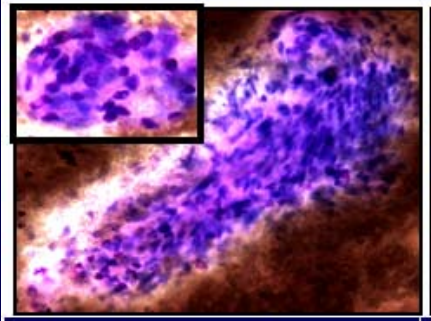
Lipomatous: LS



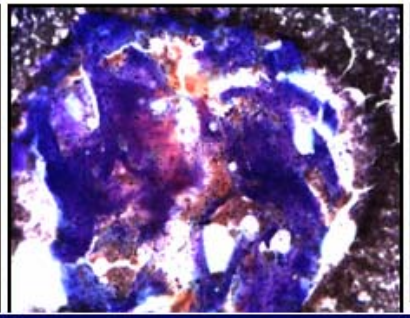
Myxoid: MLS



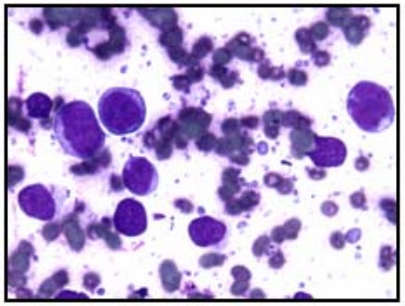
Fibrillary: MPNST



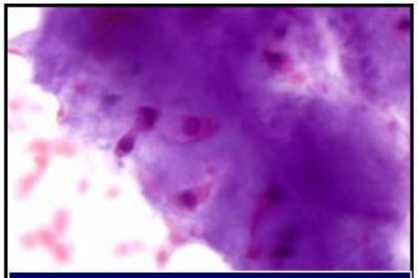
Hemorrhagic: angiosarcoma



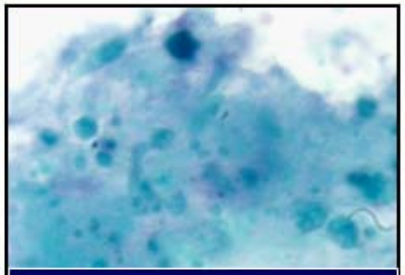
Hemorrhagic: hemangioma



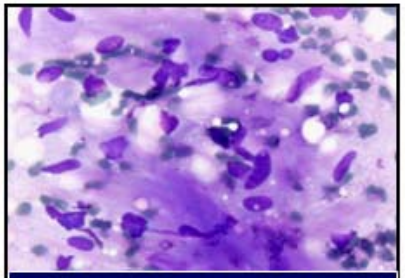
No stroma: lymphoma



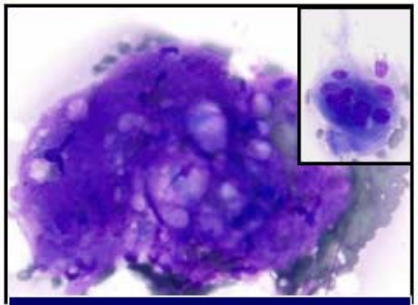
Chondroid: chonrosarcoma



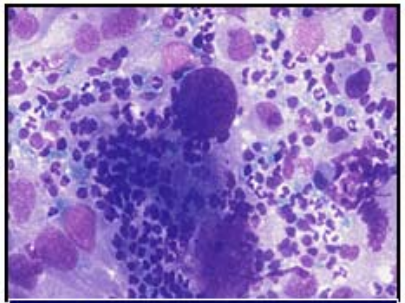
Necrotic: sarcoma



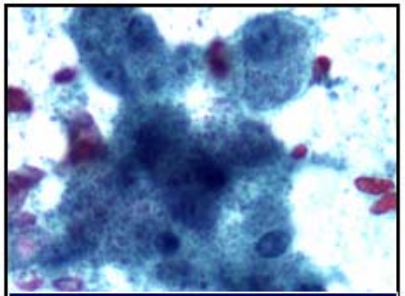
Collagenous: neurofibroma



Chondromyxoid



Inflammatory: sarcoma



Granular: Granular cell tumor

General FNA categories in Soft Tissue FNA (Geisinger & Abdul-Karim with Modifications)

Spindle Cell Lesions

- Fibromatosis
- Nodular fasciitis
- Spindle cell lipoma
- Schwannoma
- Neurofibroma

- Fibrosarcoma
- Synovial sarcoma
- Leiomyosarcoma
- MPNST
- Kaposi sarcoma
- Some MFH
- Some Angiosarcoma
- DFP

Round Cells

- Paraganglioma
- Glomus tumor
- Solitary fibrous tumor

- Rhabdomyosarcoma
- Ewing/PNET
- Neuroblastoma
- DSRCT
- PD. synovial sarcoma
- Cellular variant of EMC
- Non-Hodgkin's lymphoma

Inflammatory/Reactive Cells

- Abscess
- Granulomatous inflammation
- Proliferative fasciitis/myositis
- Focal myositis
- Fat necrosis
- Muscle regeneration

Myxoid

- Ganglion cyst
- Myxoma
- Nodular fasciitis

- Myxoid liposarcoma
- Myxoid MFH
- Myxoid chondrosarcoma
- Chordoma
- Met mucinous Ca

Lipomatous tumors

- Lipoma
- Fibrolipoma
- Chondroid lipoma
- Intramuscular lipoma
- Myelolipoma
- Hibernoma

- Liposarcoma
- Lipoblastoma

Polygonal/Epithelioid

- Rhabdomyoma
- Granular cell tumor

- Epithelioid sarcoma
- Epithelioid variants of leiomyosarcoma
- MPNST, epitheliod variant
- Angiosarcoma
- Epithelioid hemangioendothelioma
- Malignant extrarenal rhabdoid tumor
- Pleomorphic rhabdomyosarcoma
- Clear cell sarcoma
- Alveolar soft part sarcoma
- Metastatic tumors
- Some types of lymphomas

Giant Cells Lesions:

- Giant cell tumor of tendon sheath
- Pigmented villonodular synovitis
- Giant cell tumor of bone

- Myxoid MFH
- Chondroblastoma
- Anaplastic MFH
- Giant cell-rich osteosarcoma
- Pleomorphic sarcoma

Pleomorphic

- MFH
- Pleomorphic sarcomas
  - Liposarcoma
  - Rhabdomyosarcoma
  - Other sarcomas

- DFS: Dermatofibrosarcoma protuberans
- MFH: malignant fibrous histiocytoma
- MPNST: malignant peripheral nerve sheath tumor
- DSTCT: desmoplastic small round cell tumor.
- PNET: Primitive neuroectodermal tumor

- Inflammatory Lesions
- Spindle cell Lesions
- Lipomatous tumors
- Round/Polygonal Cell Lesions
- Pleomorphic Lesions
- Myxoid Lesions
- Chondroid/Osteoid Lesions
- Giant Cells Lesions

Predominance of Epithelioid cells:

Table 7 summarized the sarcomas that have can be confirmed by FISH testing.

- Rhabdomyoma
- Granular cell tumor
- Epithelioid sarcoma
- Epithelioid variants of leiomyosarcoma
- Malignant peripheral nerve sheath tumor
- Angiosarcoma
- Epithelioid hemangioendothelioma
- Malignant extrarenal rhabdoid tumor
- Pleomorphic rhabdomyosarcoma
- Clear cell sarcoma
- Alveolar soft part sarcoma
- Metastatic tumors (melanoma, carcinoma, mesothelioma)
- Some types of lymphomas.

Predominance of Round Cells:

- Rhabdomyosarcoma
- Ewing/PNET
- Neuroblastoma
- Desmoplastic small round cell tumor
- Poorly differentiated synovial sarcoma
- Cellular variant of extraskeletal myxoid chondrosarcoma
- Paraganglioma
- Glomus tumor
- Solitary fibrous tumor
- Non Hodgkin's lymphoma

Table 7 summarized the sarcomas that have can be confirmed by FISH testing.

Tumor	Genes/FISH
Alveolar soft part sarcoma	ASPL, TFE3
Clear cell sarcoma	EWSR1, ATF1
Dermatofibrosarcoma protuberans	COL1A1, PDGFB
Desmoplastic small round cell tumor	EWSR1, WT1
Ewing sarcoma/primitive neutoectodermal tumor	EWSR1, FLI1 EWSR1, ERG EWSR1, ETV1 EWSR1, FEV EWSR1, E1AF EWSR1, ZSG
Extraskeletal myxoid chondrosarcoma	EWSR1, CHN RBP56, CHN CHN, TCF12
Liposarcoma, well-differentiated	MDM2, CDK4
Liposarcoma, myxoid/round cell	CHOP, FUS
Low grade fibromyxoid sarcoma	FUS, CREB3L1 or 2
Rhabdomyosarcoma, alveolar	PAX3, FKHR PAX7, FKHR
Synovial sarcoma	SSX1 or 2, SYT

Rhabdomyosarcoma (RMS)

- Most common sarcoma in children & young adults (50% of pediatric sarcoma).
- Subtypes: alveolar, anaplastic, embryonal, pleomorphic, sclerosing, although mixtures are common.
- Children 2-6 years usually have head, neck or GU tumors
- Teenagers usually have Para testicular, trunk or abdominal tumors
- Relatively rare in adults, who often have pleomorphic and NOS subtypes
- The alveolar variant accounts for 30% of all RMS.
- Lymph node metastases of soft-tissue sarcomas are fairly rare.
- Embryonal type has markedly improved prognosis with new therapies over the last century, but not for cases of alveolar rhabdomyosarcoma.

Cytomorphology of Alveolar RMS

- Moderately to highly cellular smears.
- Loosely cohesive aggregates of **uniform, small round blue cells** with hyperchromatic nuclei and finely granular chromatin.
- Scant stromal components, may **shows myxoid stroma**.
- Scant cytoplasm with **rare cross-striations seen**.
- Favoring the alveolar variant if: small intracytoplasmic vacuoles, binucleate cells, and giant tumor cells, more cellular aspirates, some large cell component, more uniformly round to polygonal, and absence of spindle, tadpole-, or ribbon- shaped cells.
- RMS: desmin+/-, MSA+/-, MyoD+ (nuclear) and Myogenin+ (nuclear), vimentin+; CD99+/-. S100+/-; EMA-, CD45-, and CK-.
- Characteristic translocations, t(2;13)(q35;q14) and t(1;13)(p36;q14) in alveolar RMC.
- The DD includes synovial sarcoma, Ewing sarcoma/PNET.

Rhabdomyosarcoma (RMS)

- Note: some alveolar and embryonal tumors have similar gene expression (AJP 2009;174:550)

•**70% of** alveolar RMS are characterized by a chromosomal translocation, t(2;13)(q35;q14), that results in fusion of genes for two DNA-binding transcription factors, **the PAX3 gene (2q35) and the FKHR gene (13q14),** that results in abnormal cell proliferation. An alternate translocation involving PAX7 (1p36) and FKHR, t(1;13)(p36;q14), occurs in 10-20% of cases and produces a similar aberrant gene product. The latter translocation tends to occur in less aggressive tumors and in younger children.

Myogenin is a specific marker for rhabdomyosarcoma: an immunohistochemical study in paraffin-embedded tissues. Mod Pathol. 2000 Sep;13(9):988-93.

119 tumors

- 48 alveolar RMS (ARMS)
- 20 embryonal RMS (ERMS)
- one spindle cell RMS,
- 16 Ewing's sarcomas (ES),
- 6 nephroblastomas,
- 2 ectomesenchymomas,
- 7 precursor hematopoietic neoplasms
- 5 olfactory neuroblastomas
- 3 neuroblastomas,
- 6 DSRCTs
- 5 rhabdoid tumors

Nuclear staining for myogenin was noted in all 69 RMS.

- ARMS: 75 to 100% were positive,
- ERMS, rare + to 25%

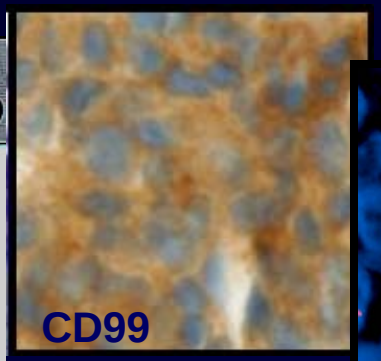
Ewing Sarcoma/Primitive Neuroectodermal tumor (PNET)

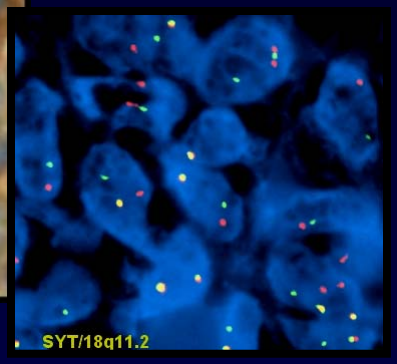
- Cellular smears
- Single and large aggregates
- Rosette-like structures
- Fairly monotonous, small round blue cells
- Immunohistochemistry:CD99 (O13/MIC2).

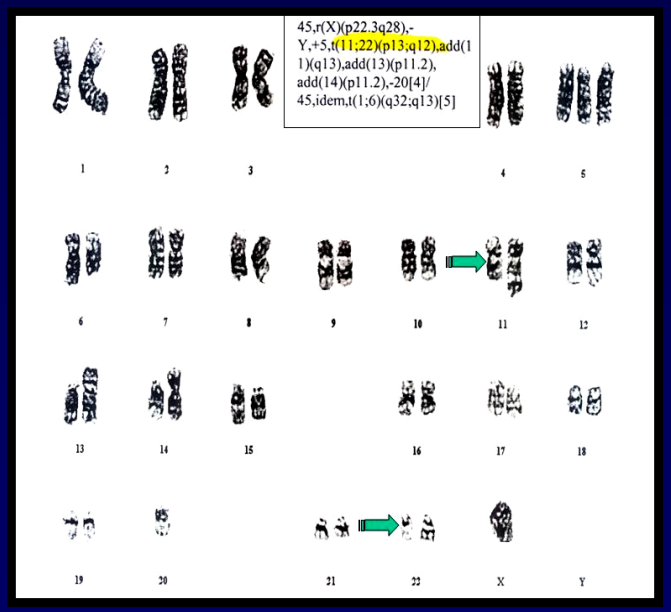
D.D.:

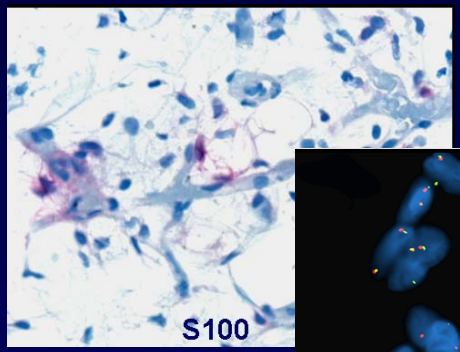
- Small cell osteosarcomas
- Rhabdomyosarcomas
- Lymphoblastic lymphomas
- Vim, desmin and myogenin, CD45, CD99, TdT

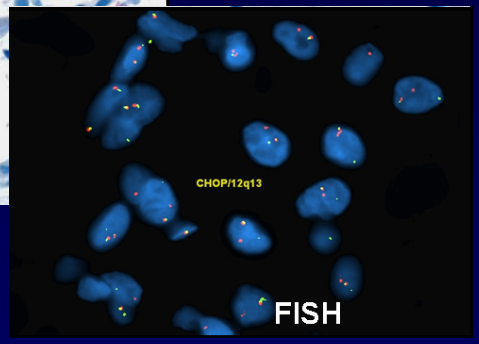
Sarcoma	Chromosomal aberration	Genes involved	Performed on FNA (Ref. No.)
ES/PNET	t(11;22)(q24;q12)	*FLI1-EWS*	64, 66
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14)	*PAX3-FKHR*	67
DSRCT	t((11;22)(p13;q12)	*WT1-EWS*	127
Synovial sarcoma	t(X;18)(p11.2;q11.2)	*SSX1-SYT*	65
		SSX''-SYT	
Clear cell sarcoma	t(12;22)(q13;q12)	*AFT1-EWS*	
EMC	t(9;22)(q22;q12)	*TEC-EWS*	68

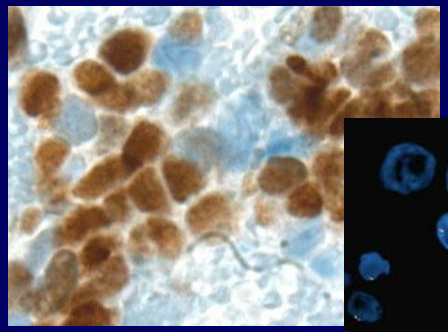


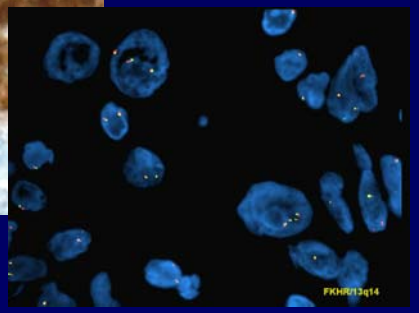












Studies	Sensitivity	Specificity	# of Cases
Layfield et al., 1986	95%	95%	N.A.
Bommer, 1997	96%	99%	450
Wakely et al., 2000	100%	97%	82
Garcia-Solano, 2000	91%	100%	107
Jorda et al, 2000	92%	99%	314
Nagira et al, 2002	92%	97%	N.A.
Kitagawa et al, 2003	100%	100%	93
Amin et al., 2003	81%	100%	N.A.
Dey et al, 2004	92%	93%	N.A.
Rekhi et al., 2007	100%	83%	127
Hirachand S., 2007	25%	100%	50
Khalbuss et al., 2010	97%	98%	1114

Table 1. Sensitivity and Specificity of Soft Tissue and Bone FNA in 12 Studies

The background:

- Clean
- Inflammatory
- Myxoid/Mucinous
- Collagenous/Fibrotic
- Cartilaginous/Osseous
- Hemorrhagic
- Necrotic background

Predominant cell type:

- Spindle Cells
- Large Round/Polygonal cells
- Pleomorphic Cells,
- Small/Round Cell
- Inflammatory-Type Cells,
- Giant-Cell Containing.

Multidisciplinary Approach

- Clinical presentation
- Radiological findings
- Cytomorphological features
- Ancillary studies: Immuno/FISH

Accuracy of Soft Tissue & Bone FNA

Original Article

Diagnostic Accuracy and Limitations of Fine-Needle Aspiration Cytology of Bone and Soft Tissue Lesions

A Review of 1114 Cases With Cytological-Histological Correlation

Walid E. Khalbuss, MD, PhD; Lisa A. Teot, MD; and Sara E. Monaco, MD

BACKGROUND: Fine-needle aspiration (FNA) cytology is increasingly being used as a diagnostic modality for soft tissue and bone lesions. These diagnoses can be challenging because of a variety of factors, including interpretation and sampling issues. This study investigates the diagnostic utility of FNA biopsy, in addition to the diagnostic pitfalls, in soft tissue and bone cytopathology. **METHODS:** We retrospectively reviewed the soft tissue and bone FNAs over a 4-year period (2004-2008), along with available ancillary studies, pathological follow-up, and clinical data. The cases with a cytologic-histologic discrepancy were then reviewed. **RESULTS:** A total of 1114 soft tissue and bone FNAs were identified. Of the 1114 aspirates, 525 (47%) were positive for malignant cells, 505 (45.5%) were benign aspirates (including 189 benign lesions/neoplasms), 37 (3.5%) were inadequate, 34 (3%) had atypical cells, and 13 (1%) were suspicious for malignancy. Of the 586 cases (53%) with follow-up, including 445 cases with histological follow-up and 141 with ancillary studies, the overall sensitivity was 96%, the specificity was 98%, the positive predictive value was 99%, and the negative predictive value was 92%. A total of 15 false negatives and 3 false positives were identified with errors because of sampling (9 cases), interpretation (7 cases), and screening (2 cases). **CONCLUSIONS:** This large series demonstrates that there can be a high sensitivity and specificity in diagnosing bone and soft tissue lesions by FNA. Our data supports prior studies in the literature in showing that FNA cytology can be a valuable method for diagnosing these lesions. ***Cancer (Cancer Cytopathol)* 2010;118:24–32.** © *2010 American Cancer Society.*

Reporting of FNA of Soft Tissue Lesions

1. Positive: for malignancy or for neoplasm
2. Negative
3. Atypical
4. Suspicious
5. Inadequate

A multidisciplinary approach

With integration of the clinical presentation, radiological findings, cytomorphological features, and ancillary studies (multidisciplinary approach), a specific diagnosis can be rendered in majority of soft tissue lesions, with accuracy greater than 90% in most publications.

The Differential Diagnoses of Soft Tissue and Bone Tumors with Spindle Cell Morphology

Benign

- Nodular fasciitis/pseudosarcomas
- Schwannoma/neurofibroma
- Spindle cell lipoma/fibrolipoma
- Leiomyoma
- Fibromatosis
- Granulomatous inflammation

Malignant

- Fibrosarcoma
- Leiomyosarcoma
- Synovial sarcoma
- Malignant peripheral nerve sheath tumors (MPNST)
- Kaposi sarcoma
- Low-grade fibromyxoid sarcoma
- Gastrointestinal stromal tumors (GIST)
- Some angiosarcoma
- Some liposarcoma
- Malignant Fibrous Histiocytoma (MFH)
- Metastatic spindle cell carcinoma
- Malignant spindle cell melanoma

FNA of Spindle Cell Lesions of Soft Tissue and Bone

Entity	Key Cytological Features
Pseudosarcoma, nodular fasciitis; myositis ossificans	No atypia, mixed cellular and background patterns and short duration (rapid growth)
Schwannoma	fishhook naked nuclei, spindle cells, Verocay bodies (palisading)
Neurofibroma	fishhook naked nuclei, spindle cells, no Verocay bodies
Spindle cell lipoma/ fibrolipoma	Mixture of mature adipose tissue and bland spindle cells in a myxoid and collagenous background.
Sarcomas	Mononuclear cells with significant atypia, marked pleomorphism, bizarre cells, mitosis, bloody or necrotic background, CK-, Vim+, HMB45-
Kaposi sarcoma	Bloody background, clusters of spindle cells with ovoid nuclei with mostly smooth contours and finely-dispersed chromatin and 1-2 small nucleoli , HHV8+
Solitary fibrous tumor	A Spindle cells and round cells in cell groups, dissociated cells and naked nuclei; CD34+
Pleomorphic/spindle cell carcinoma	Giant cells (2-10 nuclei, pleomorphic) & mononuclear cells have significant atypia, nuclear blebbing, marked pleomorphism, dyscohesive cell pattern, neutrophils within cytoplasm, bizarre cells, tumor necrosis, , CK+ Vim+/-, HMB45-, S100-,
Melanoma, pleomorphic	Atypical mononuclear and giant cells with significant atypia, marked pleomorphism, bizarre cells, discohesive cell pattern, giant nucleoli, nuclear inclusions, central grooving, CK- Vim+, HMB45+, S100+, Melan A+

FNA of Giant Cell-Containing Lesions affecting Soft Tissue and Bone

Entity	Key Cytological Features
Nodular fasciitis	Giant cells (2-10 nuclei, bland) & mononuclear cells have no atypia, uniform nuclei, mixed cell pattern, short duration, rapid growth
Fat necrosis/granulomas	Foreign body giant cells (2-10 nuclei, bland) & lipophages with no atypia, epithelioid cell, bloody or necrotic background ; PMNs & lymphocytes
Giant Cell Tumor of Tendon Sheath	Giant cells (3-50 nuclei) & mononuclear cells have no atypia; uniform nuclei; hemosiderin pigments; xanthocyte, clean or granular debris background
Giant cell tumor of bone	Giant cells (10-100 nuclei) & mononuclear cells have no atypia; uniform nuclei; no hemosiderin pigments, clean or bloody background
Sarcoma, pleomorphic	Giant cells (10-20 nuclei, pleomorphic); mononuclear cells have significant atypia and marked pleomorphism, bizarre cells, bloody or necrotic background, CK-, Vim+, HMB45-
Giant-cell-rich osteosarcoma	Giant cells (2-10 nuclei, bland, uniform, osteoclastic) & mononuclear cells have significant atypia and marked pleomorphism, bizarre cells, bloody or necrotic background, CK-, Vim+, HMB45-, osteonectin+
Melanoma, pleomorphic	Giant cells (2-10 nuclei, pleomorphic) & mononuclear cells have significant atypia, marked pleomorphism, bizarre cells, discohesive cell pattern, giant nucleoli, nuclear inclusions, central grooving, CK- Vim+, HMB45+, S100+, Melan A+
Giant cell carcinoma	Giant cells (2-10 nuclei, pleomorphic) & mononuclear cells have significant atypia, nuclear blebbing, marked pleomorphism, dyscohesive cell pattern, neutrophils within cytoplasm, bizarre cells, tumor necrosis, , CK+ Vim+/-, HMB45-, S100-,
Anaplastic Lymphoma	Giant cells (2-10 nuclei, pleomorphic) & mononuclear cells have significant atypia, marked pleomorphism, dyscohesive cell pattern, no significant reactive lymphocytes, bizarre cells, tumor necrosis, , CK- Vim+, HMB45-, S100-, CD45+, CD30+, EMA+/-; CD15+/-

Lipomatous tumors

- Lipoma
- Fibrolipoma
- Chondroid lipoma
- Intramuscular lipoma
- Myelolipoma
- Hibernoma
- Liposarcoma
- Lipoblastoma

- Inflammatory Lesions
- Spindle cell Lesions
- Lipomatous tumors
- Round/Polygonal Cell Lesions
- Pleomorphic Lesions
- **Myxoid Lesions**
- Chondroid/Osteoid Lesions
- Giant Cells Lesions

•Myxoid Lesions

- Ganglion cyst
- Myxoma
- Myxoid Nodular fasciitis
- Myxoid myositis ossificans
- Myxoid chondrosarcoma
- Myxoid liposarcoma
- Myxoid MFH
- Chordoma
- Metastatic mucinous carcinoma

The Contribution of Fluorescence In-situ Hybridization (FISH) Studies to the Fine-Needle Aspiration Biopsy (FNAB) of Soft Tissue and Bone Neoplasms.

M Bansal, M.D., G Cai, M.D., and WE Khalbuss, M.D., Ph.D.

METHOD: 862 cases of soft tissue and bone were diagnosed by FNAB at our institution. **FISH studies** were performed in **85 cases (10%)**.

RESULTS: The 85 cases with FISH studies included **42 cases of hematopoietic tumors**, **25 cases of mesenchymal tumors**, and **18 cases of metastatic breast carcinoma**. The indications for performing FISH studies were for tumor subclassification (**67 cases, 79%**) and detection of HER2/neu gene amplification (**18 cases, 21%**). The most common requested FISH studies were the **IgH gene rearrangement** for hematopoietic malignancies and **t(12;16), t(12,22)/CHOP-TLC and t(11;22)/EWSR1 for mesenchymal malignancies.**

CONCLUSIONS: advantageous as an ancillary technique in the diagnosis and management of soft tissue and bone lesions.

- Inflammatory Lesions
- Spindle cell Lesions
- Lipomatous tumors
- Round/Polygonal Cell Lesions
- Pleomorphic Lesions
- **Myxoid Lesions**
- Chondroid/Osteoid Lesions
- Giant Cells Lesions

CONCLUSIONS

- FNA of soft tissue lesions can be challenging
- Soft tissue lesions can usually be classified into general categories based on the predominant cell type and background and often a specific diagnosis can be made or suggested based on:
  - Cytomorphologic characteristics,
  - Clinicoradiographic features, and
  - Ancillary studies.

Khalbuss · Parwani
Cytopathology of Soft Tissue and Bone Lesions

Essentials in Cytopathology
Series Editor: Dorothy L. Rosenthal

Cytopathology Soft Tissue and Bone Lesions by Walid E. Khalbuss and Anil V. Parwani will fulfill the need for an easy-to-use and authoritative synopsis of soft tissue and bone cytopathology. This volume, part of the Essentials in Cytopathology book series, fits into the lab coat pocket and is ideal for portability and quick reference. Each volume in the series is heavily illustrated with a full color art program, while the text follows a user-friendly outline format.

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