Soft Tissue Cytopathology: Coupling Morphology & Ancillary Testing for Diagnostic Accuracy
“I don't know any other pathologists who'd diagnose soft tissue lesions on cytology.”

ESOTERIC
(somewhat)
CONTROVERSIAL
S.T. FNA - Indications

• Diagnosis of a New Soft Tissue Mass
  – neoplasm
    • benign
    • malignant
  – inflammatory
  – non-neoplastic lesion

• Diagnosis of Metastatic/Locally Recurrent Malignancy
S.T. FNA - Limitations

• Sampling Error
  – Operator Dependent

  – Lesion Characteristics. FNA of soft tissue does not work very well when:
    • mass is too small
    • mass is too large
    • mass is extremely sclerotic/fibrotic
    • mass is a vague swelling or induration rather than one with discrete edges
    • mass is really cystic
    • mass has undergone a “Geode” effect
Barriers To Definitive FNA Diagnoses

- Procedural performance
- Experience/exposure to soft tissue tumors
- Sampling error
  - Tumor heterogeneity
- Lack of (minimal) architectural features
  - Spatial relationships
  - Neoplasm border
    - Pushing/infiltrative
    - Capsule
  - Patterns
  - Vasculature
- Cytomorphologic overlap
Clinical/Radiographic Features Helpful in FNA Soft Tissue Tumor Diagnosis

- **size:** only 5% of benign s.t. masses are > 5 cm.
- **location:**
  - most malignancies (60-70%) are deep, not superficial
  - only 1% of benign s.t. tumors are deep
  - e.g. 70% of retroperitoneal s.t. tumors are malignant
  - e.g. only 15% of hand & wrist lesions are malignant

- **MR features:**
  - sarcomas have a high T2 signal intensity, but so can some benign tumors
  - sarcomas are typically heterogeneous on T1 weighted images
Soft Tissue FNA - categories

- Spindle cell dominant lesions
- Stromal dominant lesions
- **Large** rounded/epithelioid cell lesions
- **Small** rounded cell lesions
- Pleomorphic lesions
Spindle Cell Dominant Lesions
Fibromatosis

- Superficial
  - Plantar/ Palmar / Penile / Knuckle Pads
- Desmoid-Type Fibromatosis
  - Abdominal Wall
  - Extra-Abdominal
  - Intra-Abdominal (Mesenteric/Pelvic)
fibromatosis
fibromatosis
fibromatosis – atrophic sk muscle
fibromatosis
Nodular Fasciitis

- 20-50 yrs.
- common, subQ
  - rapid growth
  - self-limited
  - reactive process
- upper extremities
- solitary
  - well-circumscribed
  - fibroblasts/
    myofibroblasts
  - SMA, MSA, calponin
- < 2% recur
nodular fasciitis
33 pts.; 9 involved head & neck

91% spindle cells, 30% polygonal cells, 60% ‘tissue culture’ appearance

4/9 (44%) dx = NF, consistent with NF

4/9 (44%) dx = spindle cell lesion

1/9 dx = mesenchymal tissue

6% of all 33 cases dx = malignant
myxoid change in NF
Schwannoma

discussed elsewhere
Spindle Cell Smears - Malignant

- Synovial Sarcoma
- Leiomyosarcoma
- MPNST
- DFSP
- Low-Grade Fibromyxoid Sarcoma
- GIST
“Molecular testing has the potential to reshape the practise of cytopathology and may bring a renaissance for non-gynaecological cytology.”

Slater S. Guidance for non-gynaecological cytology – a platform for the future. 

*Cytopathology* 2009; 20:279-80 (ed.)
Spindle Cell Malignancies That CANNOT / OR ONLY RARELY Be Diagnosed Reliably Using FNA Smears Alone

- synovial sarcoma
- MPNST
- GIST
- L-G leiomyosarcoma
- angiosarcoma
- low-grade fibromyxoid sarcoma
- DFSP
Spindle Cell Malignancies That MAY Be Diagnosed Reliably Using Smears And Ancillary Methods

➢ synovial sarcoma
➢ MPNST
➢ GIST
➢ L-G leiomyosarcoma
➢ angiosarcoma
➢ low-grade fibromyxoid sarcoma
➢ DFSP
Ancillary Methods

- Immunohistology
  - most common
- FISH
- PCR
- NGS

- Cytogenetics
- Electron Microscopy
Synovial Sarcoma

- 4th most common ST sarcoma
- adolescent – young adults
- t(X;18)(p11;q11)
  - fusion of 2 genes
  - SYT @ 18q11; SSX @ Xp11
- biphasic, monophasic, p-d
- IHC: TLE-1 relatively sens/spec

- cytomorphology
  - high cellularity
  - clusters + single cells
  - extreme uniformity
  - oval, rounded, spindle nuclei
  - scant, wispy cytoplasm
synovial sarcoma
synovial sarcoma
Cytohistologic Correlations in 56 Synovial Sarcomas in 36 Patients: The Institut Curie Experience

Jerzy Klijianenko, M.D., 1* Jean-Michel Caillaud, M.D., 2 Réal Lagacé, M.D., F.R.C.P.C., 3 and Philippe Vielh, M.D., Ph.D. 1

- 41% correctly diagnosed as SS
  - 21/36 (58%) primary
- 53.7% misdiagnosed as another sarcoma
- 5.1% non-diagnostic
- 2 cases (4%) cytogenetic analysis

Syn S \([n=17]\)†

- CCS (1)
  - EWSR1+
- actual FNA Dx
  - SS [14, 82%]
- susp. myxoid
  - LPS (1) *
- malignant
  - (1)*

† 2005-16

unpublished data

* no ancillary test
Syn S \([n=17]^{†}\)

- CCS EWSR1+
- actual FNA Dx
  - SS \([14, 82\%]\)
    - primary \((11)\)
      - (all SS18+)
    - metastatic \((3)\)
      - SS18+, smear + CB \((1)\)

- susp. myxoid LPS *
- malignant*

\(*\) no ancillary test

\(^{†}\) 2005-16
Syn S \([n=17]^{\dagger}\)

- CCS EWSR1+
- actual FNA Dx
  - SS [14, 82%]
    - primary (11)
      - (all SS18+)
        - smear only (2)
        - smear & CB (5)
        - CB only (4)
    - metastatic (3)
      - SS18+, smear + CB (1)

- susp. myxoid LPS *
- malignant*

\(^{\dagger}\) 2005-16

* no ancillary test
MPNST

• 25 y/o man: 14 cm. left buttock mass x 4 months.
• Hx of NF-1
• cytomorphology
  – high cellularity
  – clusters + single cells
  – extreme uniformity
  – oval, round, spindle nuclei
  – ± serpiginous nuclei
  – scant cytoplasm
• negative: S100, SOX10
• positive: EGFR, Ki-67 >20%
when one encounters a new patient without a history of NF-1 or without knowledge that the neoplasm is in proximity to, or appears to arise from, a major nerve, a specific diagnosis is exceptionally difficult. **This is because the cytomorphologic overlap with other sarcomas is too pronounced.** The results of the current study demonstrate that features espoused by others (including elongated slender, wavy, or hook-shaped nuclei; focally pronounced nuclear atypia; bizarre giant cells; and fibrillary metachromic stroma) are “soft signs” and are not categorically specific of an MPNST.
GIST

- adults, 50-60 yrs.
- most common sarcoma
  - most common mesenchymal tumor of the gut

~ 25% malignant

- spindle, epithelioid, pleomorphic (rare)

- ancillary studies:
  - CD34, CD117, DOG1
  - mutation analysis
GIST
GIST [n=67]

- favor GIST [n=3]
  - primary, no CB

- non-diagnostic [n=1]
  spindle cell neoplasm
  [n=1]
GIST [n=67]

- actual FNA Dx
  - GIST [n=62] (93%)
- favor GIST [n=3]
  - primary, no CB
- non-diagnostic [n=1]
  - spindle cell neoplasm [n=1]

unpublished data

2005-16
GIST [n=67]

- GIST [n=62]* (93%)
- favor GIST [n=3] primary, no CB
- non-diagnostic [n=1] spindle cell neoplasm [n=1]

60 primary; 2 mets
*61 confirmatory IHC
1 no IHC (met)

unpublished data

2005-16
66 y/o man. R thigh mass
spindle cell melanoma
spindle cell melanoma
Stromal Dominant Lesions

- Myxoma / Ganglion
- Myxoid Neurofibroma
- Myxoid Liposarcoma
- Myxofibrosarcoma
- Extraskeletal Myxoid Chondrosarcoma
- Chordoma
Myxoid LPS

• peak: 4th-5th decade
• 3 major cytologic criteria:
  – ramifying delicate capillaries producing so-called "chicken-wire" appearance
  – "myxocellular" clusters distributed as discrete fragments rather than a "film" smeared and
  – uni-vacuolated lipoblasts, usually signet ring type, occ. multivacuolated
myxoid LPS
Myxoid liposarcoma: Fine-needle aspiration cytopathology in the molecular era. A report of 24 cases

Paul E. Wakely Jr., MD*, Ming Jin, MD, PhD

- 24 cases; 21 pts.
- 67% thigh, 71% primary.
- M:F = 1.1:1
- 16 cases DDIT3 [t(12;16) or t(12;22)] performed (FISH)
  - 13 + for DDIT3 (81%)
  - 3 unsatisfactory
Myx LPS [n=25]

actual FNA Dx

Myx LPS [22, 88%]

primary [16]

DDIT3+ [11]

smear only (4)

smear + CB (4)

recurrent [5]

DDIT3 [2]

CB only (3)

metastatic [1]

DDIT3 [1]

susp Myx LPS [1]*

* no ancillary test
Chordoma

- 40 - 60's.
- arises along the spinal axis
  - derivation from remnants of the developing notochord
- sacrococcyx, clivus
- pan-cytokeratin EMA S-100 brachyury
Chordoma – FNAB sites 2017

- back
  - 2

- sacrum/buttock
  - 6

- neck
  - 3

- anterior tibia
  - 1 (met)

- humerus
  - 1

unpublished data
chordoma
Extraskeletal Myxoid Chondrosarcoma

- < 3% of ST sarcomas
- 35-60 yrs.
- tissue pathology
  - multilobulated pattern in tissue
  - thin to opaque myxoid stroma
  - linear cords or flat aggregates of cells
  - isomorphic round to oval nuclei
  - moderate amount of cytoplasm

- FISH probes
  - \textit{EWSR1} (50-70%)
  - \textit{NR4A3} (100%)
Abnormal Break

EWSR1
EMC [n=20]

actual FNA Dx

EMC [n=19, 95%]

primary [14]

FNA only [10]

unpublished data

recurrent [2]

concurrent CNB [4]

metastatic [3]

susp. EMC [n=1]
EMC \( [n=20] \)

**EMC \( [n=19, 95\%] \)**

- **primary \( [14] \)**
  - **FNA only \( [10] \)**
    - +NR4A3 \( [1] \)
    - neg. EWSR1
    - FISH not done \( [2] \)
  - +EWSR1 \( [1/2] \)
    - +NR4A3 \( [1] \)
    - neg. EWSR1
    - FISH not done \( [2] \)

- **recurrent \( [2] \)**
  - concurrent CNB \( [4] \)
  - +EWSR1 \( [5/7] \)
    - +NR4A3 \( [1] \)
    - neg. EWSR1
    - FISH not done \( [2] \)

- **metastatic \( [3] \)**
  - +EWSR1 \( [1/2] \)
    - +NR4A3 \( [1] \)
    - neg. EWSR1
    - FISH not done \( [2] \)

- **susp. EMC \( [n=1] \)**
Large rounded/epithelioid cell lesions – benign

- Lipomatous Tumors
- Fat Necrosis
- Granular Cell Tumor
- Rhabdomyoma, adult
- GCTTS
Benign Lipomatous Lesions

- Lipoma
- Hibernoma
- Fat Necrosis
fat necrosis
fat necrosis
fat necrosis
Large rounded/epithelioid cell lesions - malignant

- Plasma cell myeloma, extramedullary
- Lymphoma, large cell
- Alveolar soft part sarcoma
- Clear cell sarcoma
- Epithelioid sarcoma
- Any sarcoma with epithelioid features
Clear Cell Sarcoma, soft parts

- rare, young adults
- sites
  - extremities
  - rare in H&N
- IHC identical to melanoma
- t(12;22)(q13;q12)
  - EWSR1 +
- metastases common
- 10 yr. survival, 33%
clear cell sarcoma
Epithelioid Sarcoma

- rare, wide age range
  - > 70% 10-40 yrs.
- distal extremity
  - > 60% fingers, hand
  - volar surface
- painless, firm, slow-growing
- mets to lymph nodes
- lacks INI1/SMARCB1

- 5-yr. survival 40-60%

35 y/o, ♂
epithelioid sarcoma
epithelioid sarcoma
Small rounded cell lesions

- Rhabdomyosarcoma
- Ewing Sarcoma/ PNET, extra-osseous
- Mesenchymal Chondrosarcoma
- Desmoplastic Small Round Cell Tumor
- Lymphangioma
- Lymphoma
- Metastatic
  - Small Cell Neuroendocrine Carcinoma
Extra-Osseous Ewing Sarcoma
Ewing Sarcoma
Ewing Sarcoma – ‘tigroid’
Abnormal Break
Tumors with *EWSR1* rearrangement

- Ewing/PNET family
- desmoplastic SRCT
- extraskeletal myxoid chondrosarcoma
- clear cell sarcoma, soft parts
- clear cell sarcoma-like tumor of GI tract
- primary pulmonary myxoid sarcoma

- myxoid liposarcoma
- hyalinizing clear cell CA
- angiomatoid fibrous histiocytoma
- soft tissue myoepithelioma
- angiosarcoma
- LGFMS (Evans tumor)
- sclerosing epithelioid fibrosarcoma
Pleomorphic Cell Lesions

- Undifferentiated pleomorphic sarcoma (aka MFH)
- Pleomorphic sarcomas
  - LMS, LPS, RMS, MPNST
- Epithelioid sarcoma
- Pleomorphic lipoma
- Schwannoma with ‘ancient’ change
- Radiation-induced atypia
77 y/o ♀. R arm. UPS, high-grade
UPS, 71 y/♂. posterior thigh
• 107 aspirates/ 98 pts.
• 13-90 yrs. ; M = F
• 10 cases non-diagnostic
• sensitivity = 94%
• PPV = 97%
• 71% Pr; 23% Re; 75 mets

• 54: H-G sarcoma
  – 8 myxofibrosarcoma
  – 8 osteosarcoma
  – 5 MPNST
  – 5 LMS
  – 4 Ewing/ 4 LPS/ 2 EpS/ 1 AngioS

• 88% SP confirm; 3 FP dx

CONCLUSIONS. A cytopathologic diagnosis of HGS was found to be accurate in 88 of 97 cases (91%) with follow-up. A FNA biopsy diagnosis of HGS appears to be clinically reliable in a high percentage of cases when used in close conjunction with the orthopedic team. Cancer (Cancer Cytopathol) 2007;111:491–8. © 2007
pleomorphic lipoma
pleomorphic lipoma
Soft Tissue FNA - categories

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REFERENCES
