Mass General Brigham

Challenging Cases and Lessons Learned Virtual Microscopy 2

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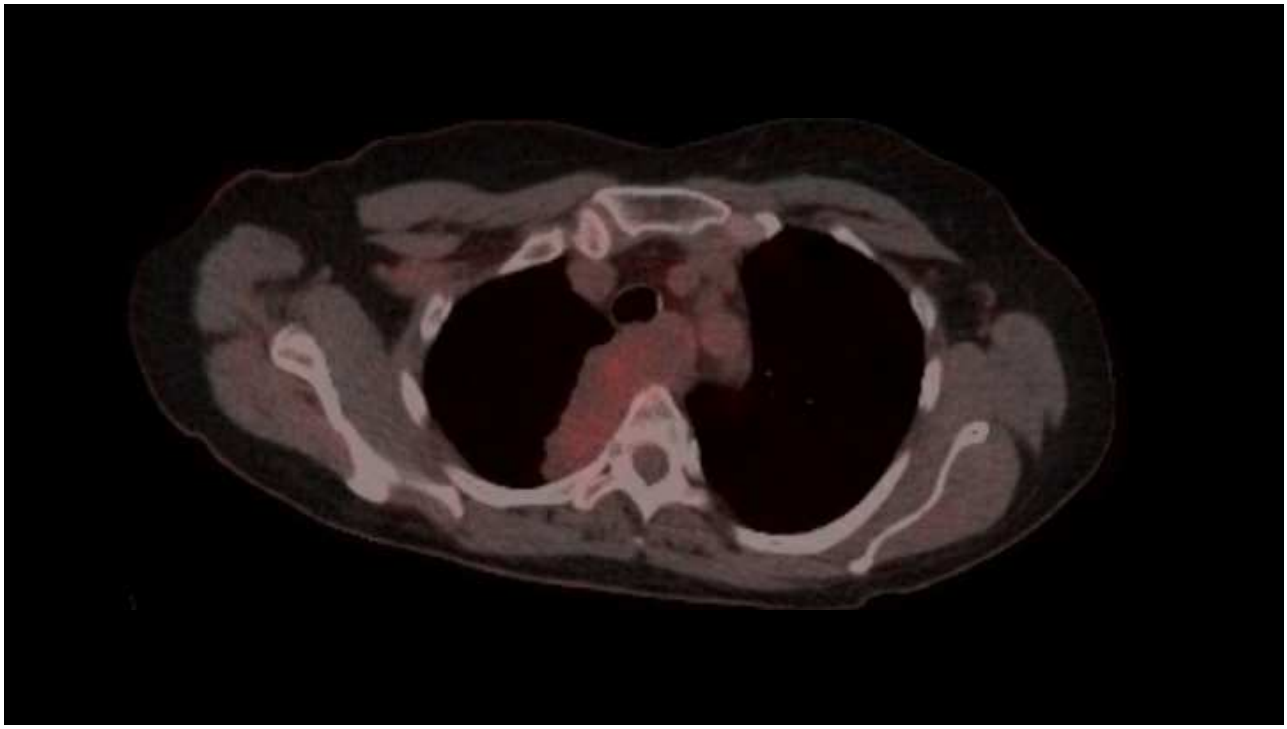
ADVANCES IN CYTOLOGY AND SMALL BIOPSIES

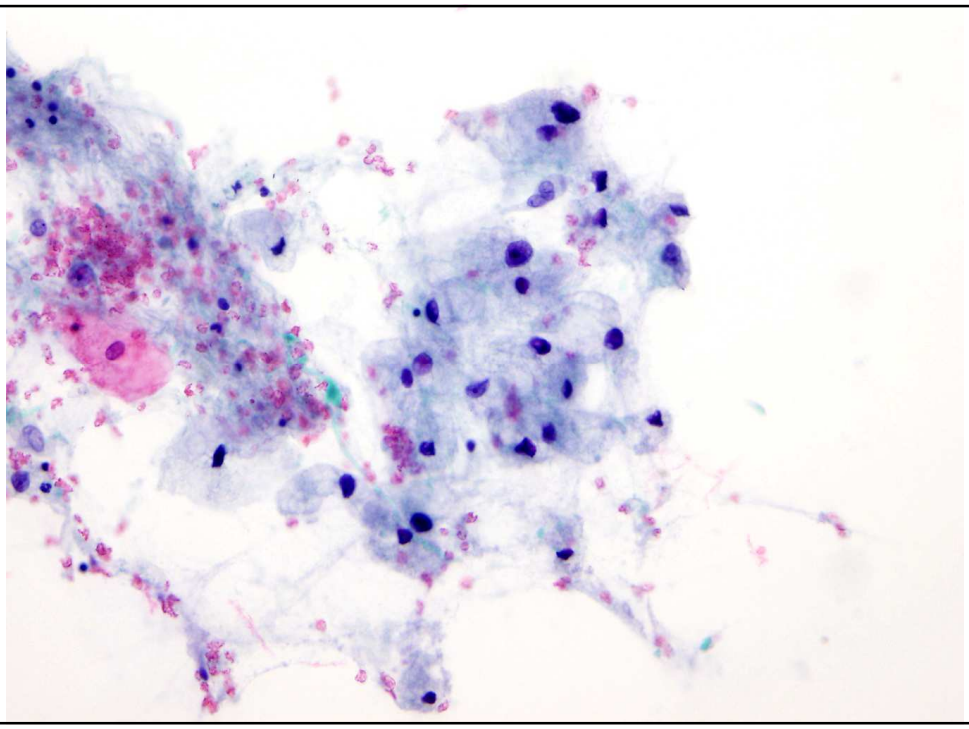
68 y/o female with posterior mediastinal and pancreatic mass on CT

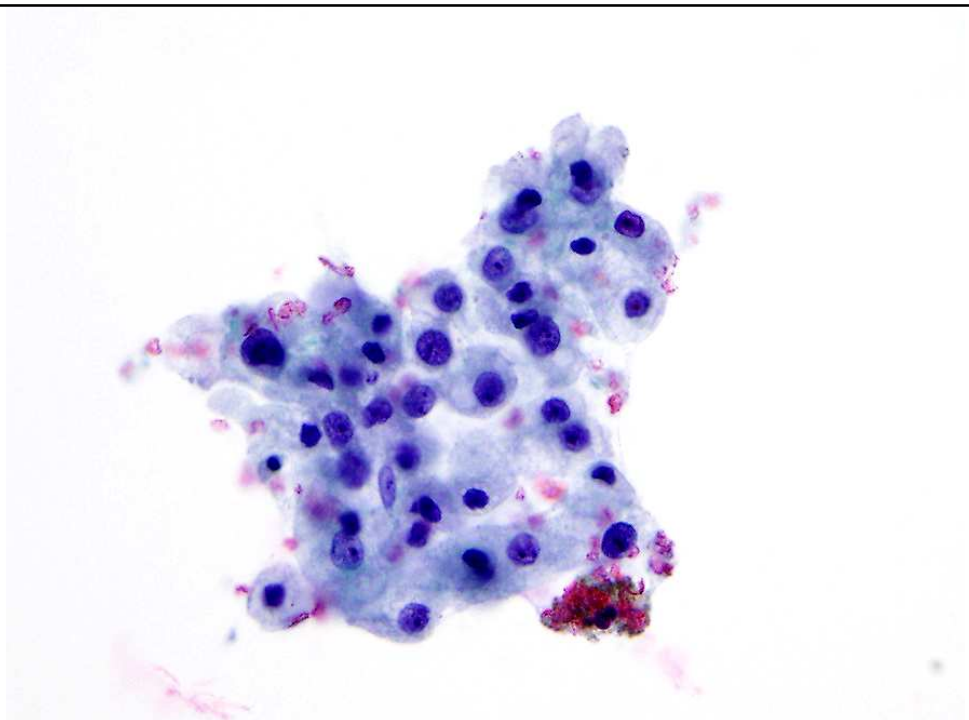
David Hwang MD
6/13/2023

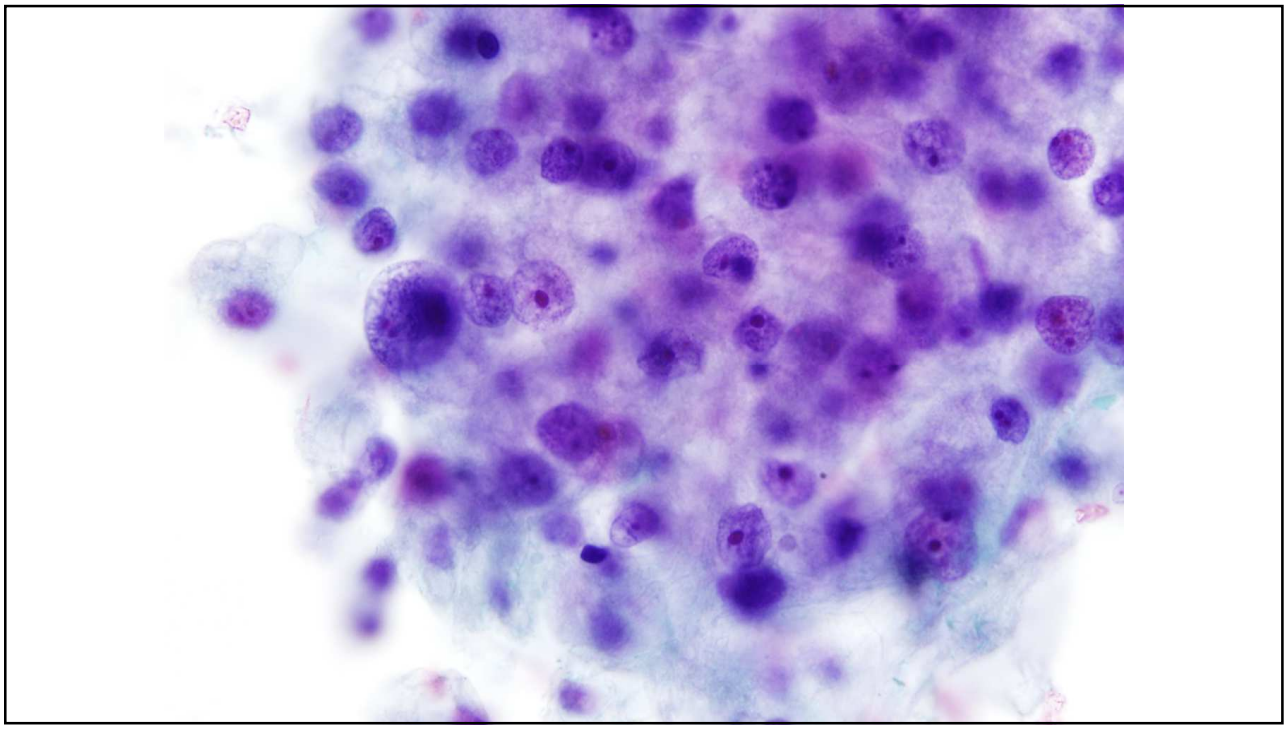
History

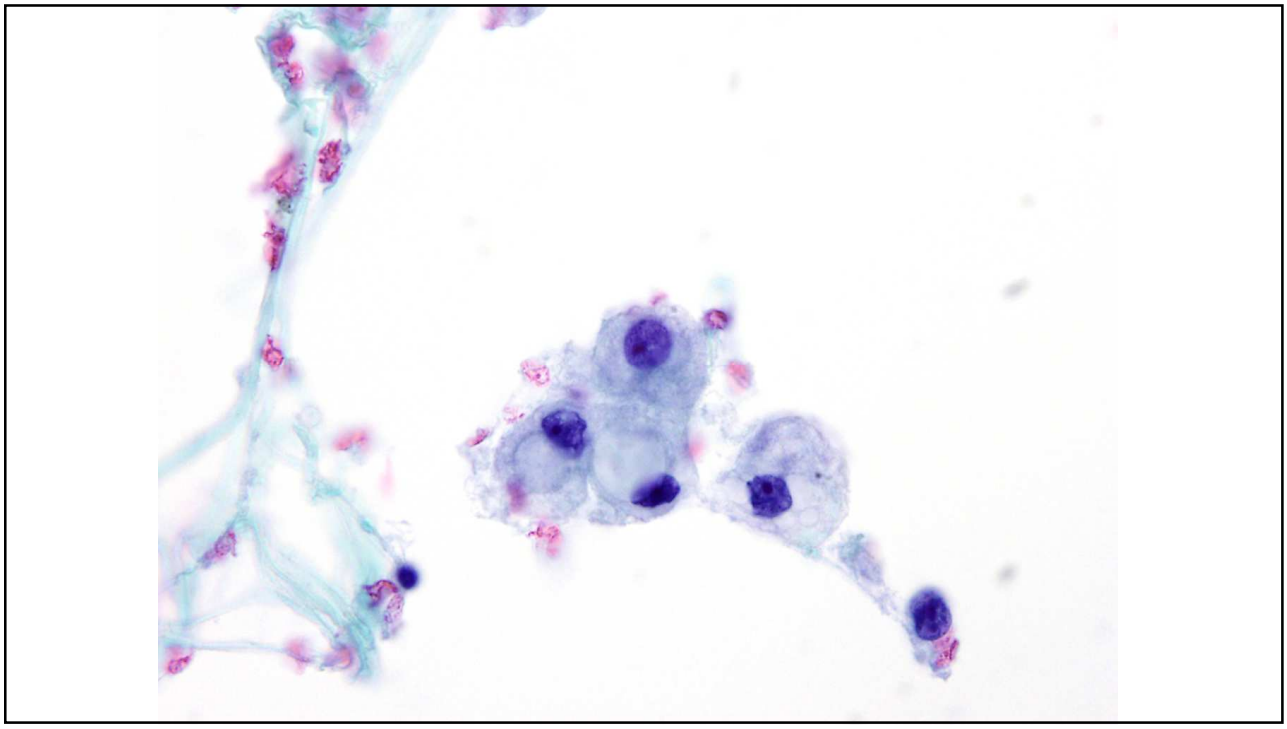
- 68 y/o female with posterior mediastinal mass discovered incidentally during work up for back pain after a fall
- CT chest revealed 6.9x4.9x4.4 cm mass abutting the trachea and esophagus
- CT abdomen pelvis showed a 1.2 cm elongated low-density abnormality in the head of the pancreas
- Initial clinical concern for duplication cyst
- Patient underwent EUS biopsy









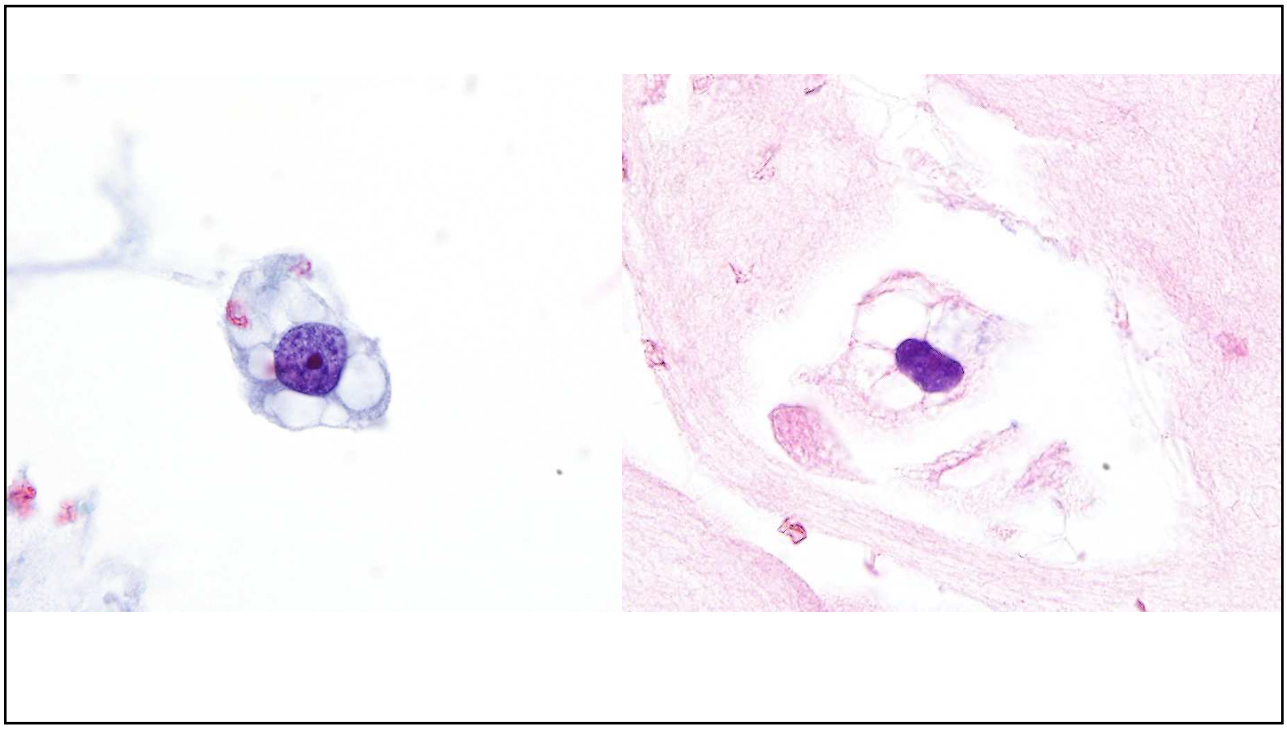


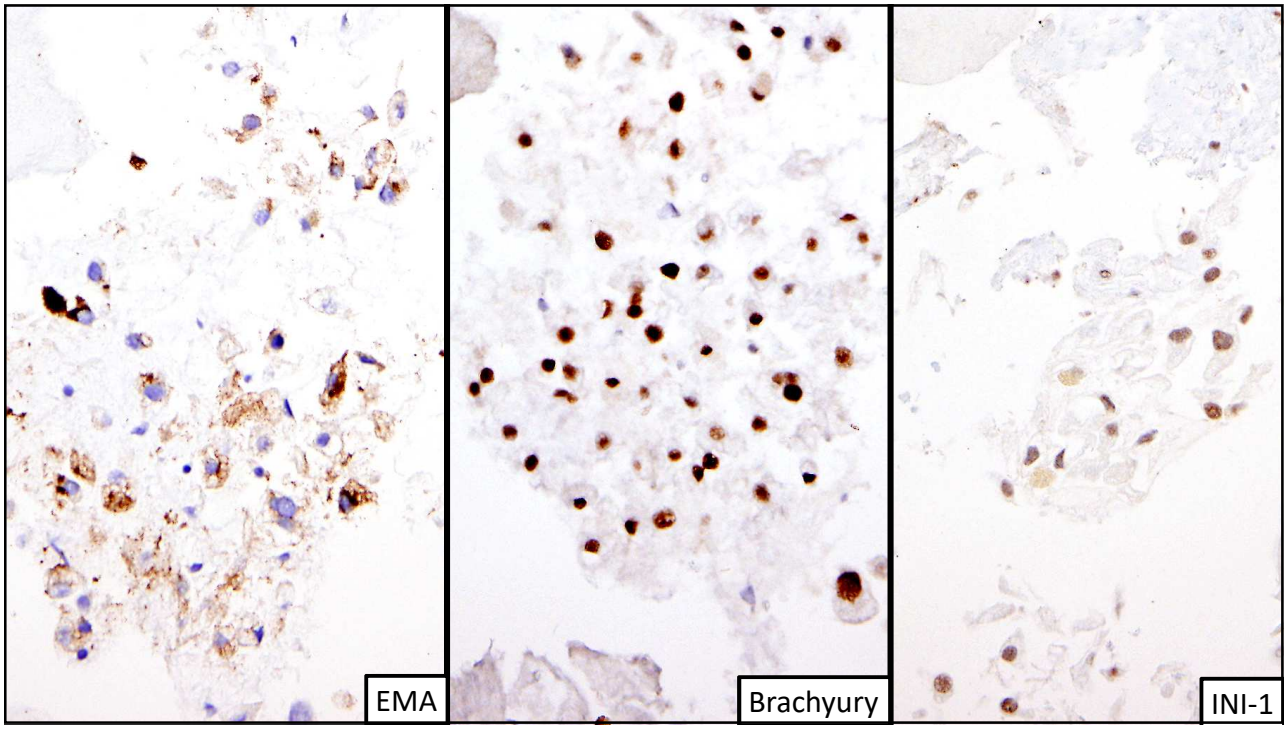
Initial Immunohistochemical Studies

- Positive: AE1/AE3
- Negative: CK7, CK20, TTF1, p40, S100, PU.1

Preliminary Cytologic Diagnosis

NEOPLASTIC CELLS PRESENT
FAVOR ADENOCARCINOMA




EMA
Brachyury
INI-1

Final Cytologic Diagnosis

MALIGNANT CELLS PRESENT

APPEARANCE MOST CONSISTENT WITH CHORDOMA

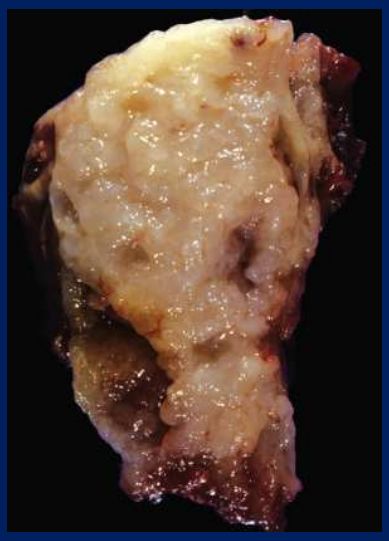
Immunohistochemical studies

Positive: AE1/AE3, brachyury, EMA (focal), INI-1 (retained)

Negative: CK7, CK20, TTF1, p40, S100, PU.1, PAX8, SALL4

Chordoma

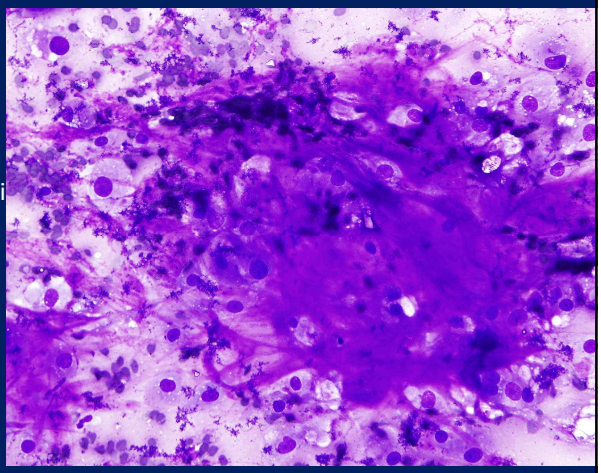
- Accounts for ~5% of malignant bone tumors
- Typically presents from the 4th-8th decade of life
- Thought to arise from notochordal remnants
  - Express brachyury, S100, keratins
- Almost always restricted to axial skeleton
  - ~50% arise from sacrum
  - ~35% skull base
  - Thoracic spine involvement very rare
- Typically a destructive/lytic lesion on imaging with soft tissue extension



Czerniak B, Dorfman and Czernieak's Bone Tumors (2016)

Chordoma Cytologic Features

- Conventional:
  - Abundant mucoid material
  - Epithelioid cells
    - Large vacuolated cells/physaliferous cells
    - Smaller rounded epithelioid cells with eosinophili to granular cytoplasm
- Chondroid Chordoma
  - Hyaline cartilage like matrix
- Dedifferentiated Chordoma
  - High-grade sarcoma juxtaposed with conventional chordoma



Differential Diagnosis

- Metastatic Carcinoma
  - S100 and brachyury negative
- Chondrosarcoma
  - Keratin and brachyury negative
- Myxopapillary ependymoma
  - GFAP positive, negative keratins and brachyury
- Soft tissue myoepithelial tumors
  - Brachyury negative

Lessons Learned

- Location:
  - Thoracic spine is the least common site for chordoma
- Unusual presentation:
  - Chordomas of the thoracic spine are frequently well circumscribed and often are not associated with destructive bone lesions
  - Matrix material often obscured in alcohol preparations
- Poorly-differentiated Chordoma
  - Aggressive subset that occurs predominantly pediatric patients/young adults
  - Prominent nuclear pleomorphism, abundant eosinophilic cytoplasm, may have rhabdoid morphology
  - Lack conventional physaliferous cells and have minimal myxoid stroma
  - Increased mitotic rate
  - Characterized by absence of SMARCB1/INI-1 expression

Shih AR, et al. Mod Path (2018) **31**: 1237

Virtual Microscopy Case

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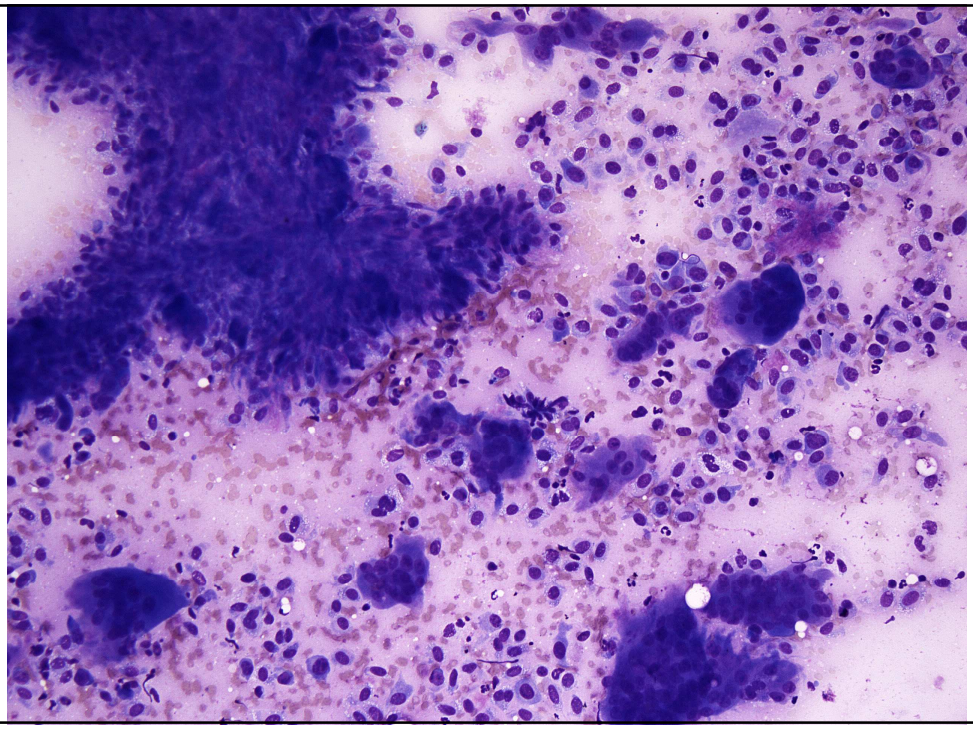
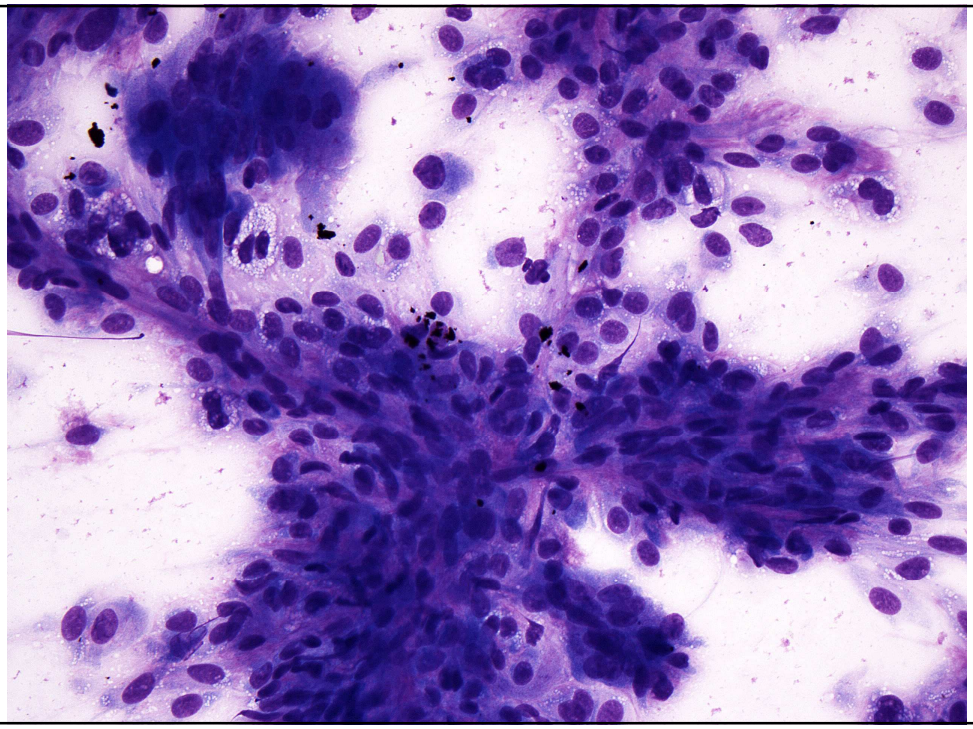
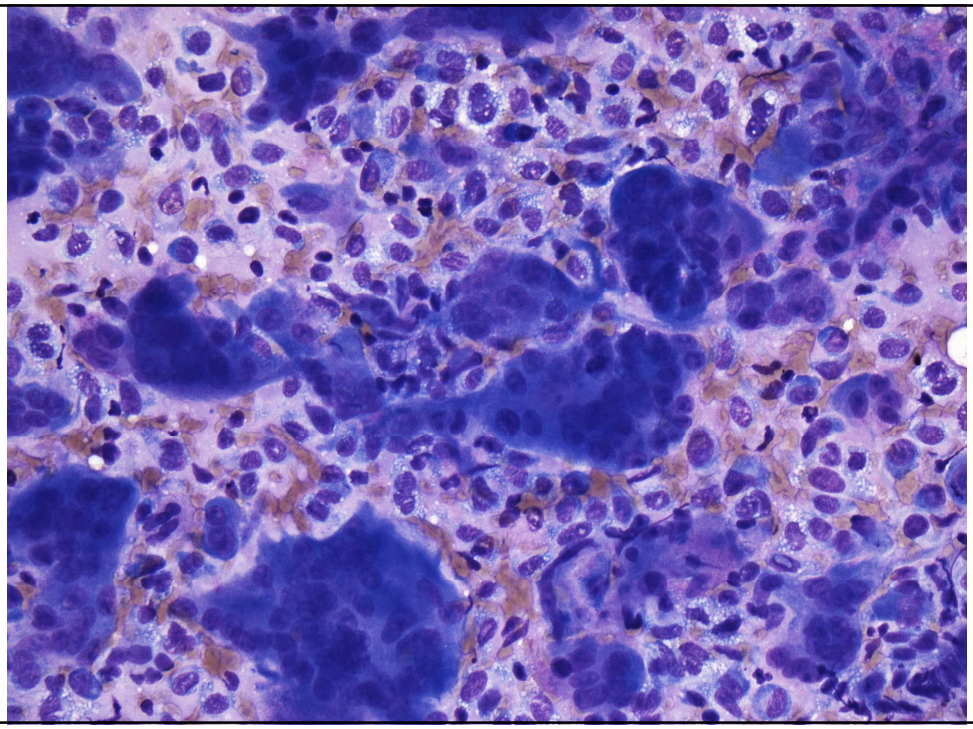
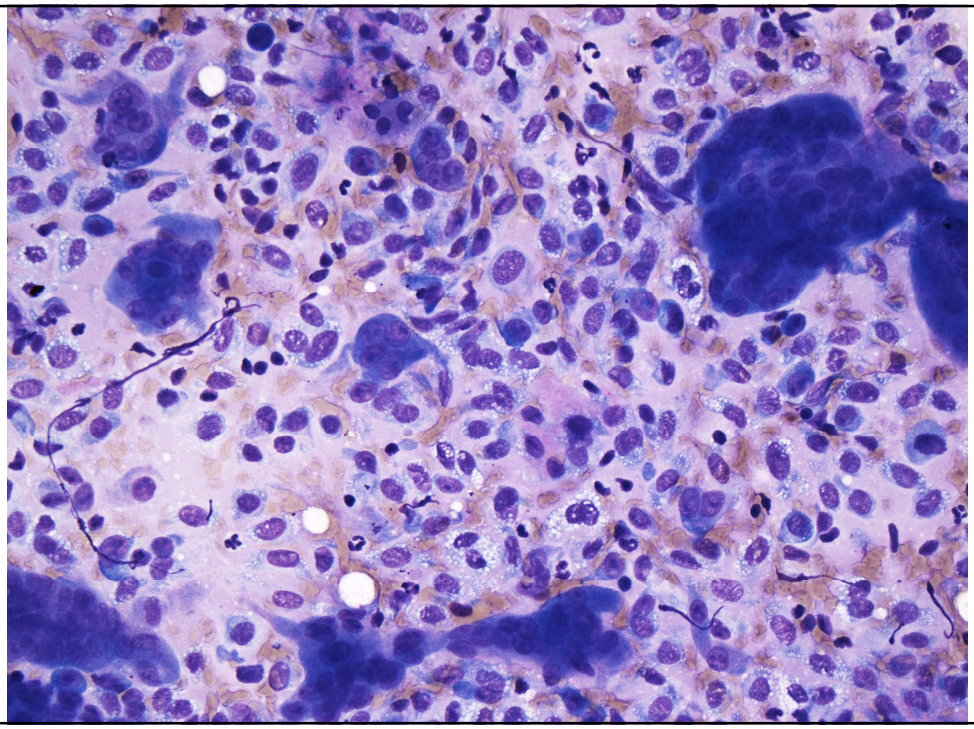
Clinical History

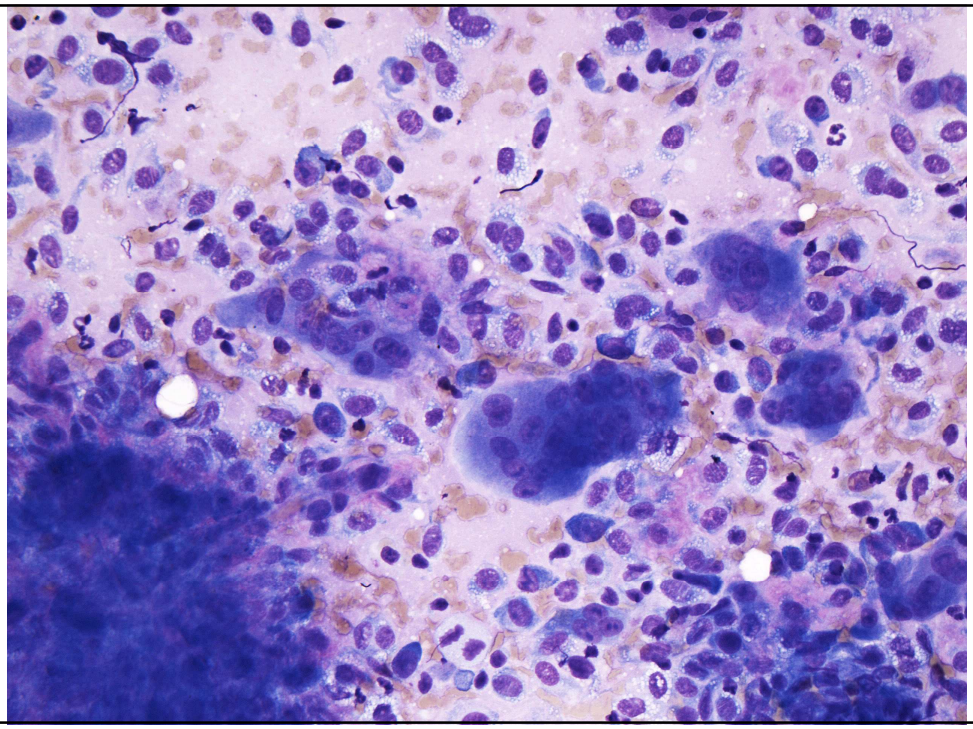
- 41-year-old woman with a right upper thigh mass.



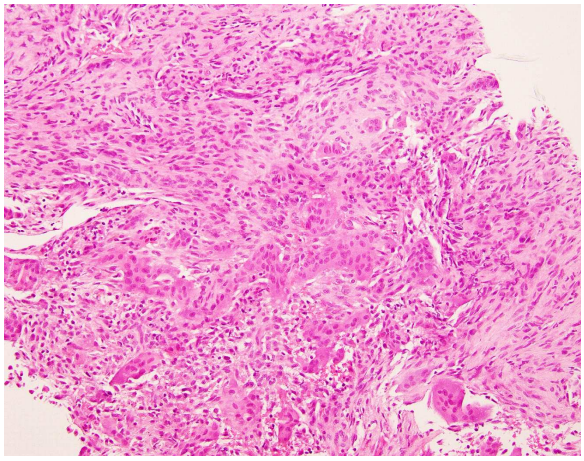


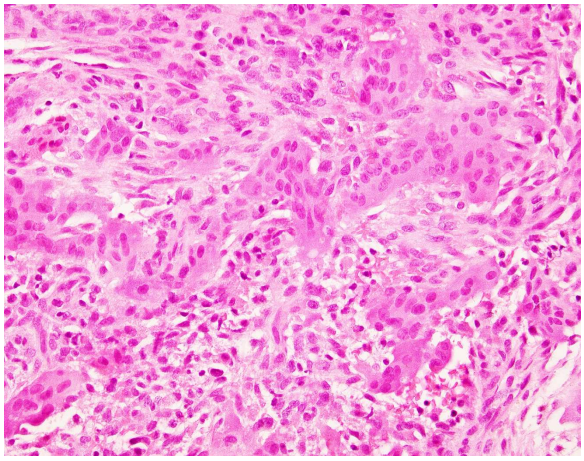






Concurrent Core Biopsy





Diagnosis?

A. Tenosynovial giant cell tumor
B. Aneursymal bone cyst, solid-type
C. Giant cell tumor of soft tissue
D. Giant cell tumor of bone
E. Giant cell-rich osteosarcoma
F. Need more information

Giant-Cell Rich Tumors

- Generally refers to predominance of osteoclast-like giant cells
  - But the lesional cells are the background cells
- The differential diagnosis depends on anatomic site
  - Soft tissue vs osseous primary
  - Review radiographic features (especially for bone lesions)
- Helpful morphologic features to assess:
  - Cell populations
  - Cytologic atypia and pleomorphism
  - Extracellular matrix (e.g. myxoid, osteoid, chondroid)

More Clinical Information

- Patient noticed it one month prior, palpable but painless
- 1.9 x 1.8 x 1.3 cm mass within the subcutaneous tissues within the lateral right thigh; abuts the fascia overlying the vastus lateralis muscle
- Radiographic findings are suggestive of a vascular malformation
  - MRI: T1 isointense, T2 hyperintense and heterogeneous; multiple feeding vessels

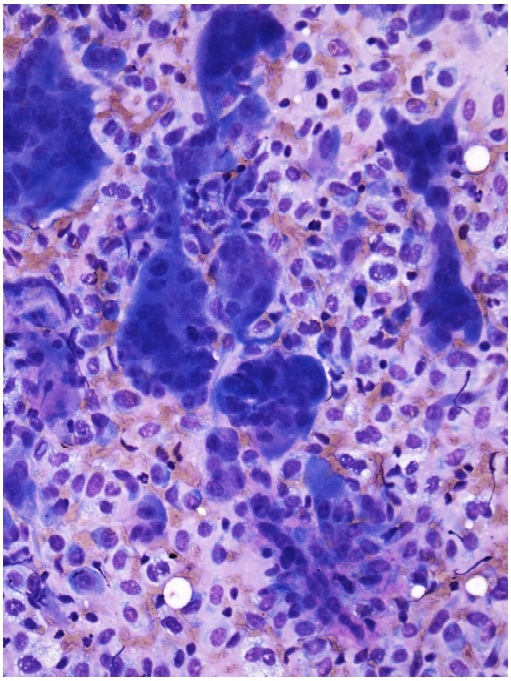
Giant Cell-Rich Tumor: DDX in Soft Tissue

Tumor Type	Characteristic Features
Tenosynovial giant cell tumor	Admixed foamy histiocytes, hemosiderin deposition
Nodular fasciitis	Rapid onset and growth, spindled myofibroblasts, inflammatory cells; giant cells tend to be sparse
Giant cell tumor of soft tissue	Mononuclear cells, abundant giant cells with many nuclei
Aneurysmal bone cyst*	Myofibroblasts, hemosiderin-laden macrophages, bone fragments Solid variant –hypercellular, may see abundant giant cells
Giant-cell rich osteosarcoma*	Osteoid matrix, pronounced atypia and pleomorphism
Other giant-cell rich sarcomas (e.g. leiomyosarcoma, dedifferentiated liposarcoma)	Atypia and pleomorphism, recognizable conventional areas
Giant-cell rich carcinoma	Atypia and pleomorphism, clinical history

**Can arise as both extra-osseous and primary bone lesions*

Our case

Tumor Type
Tenosynovial giant cell tumor
Nodular fasciitis
Giant cell tumor of soft tissue
Aneurysmal bone cyst, solid-type
~~Giant-cell rich osteosarcoma~~
~~Other giant-cell rich sarcomas (e.g. leiomyosarcoma, dedifferentiated liposarcoma)~~
~~Giant-cell rich carcinoma~~



Biopsy Diagnosis

NEOPLASTIC CELLS PRESENT.

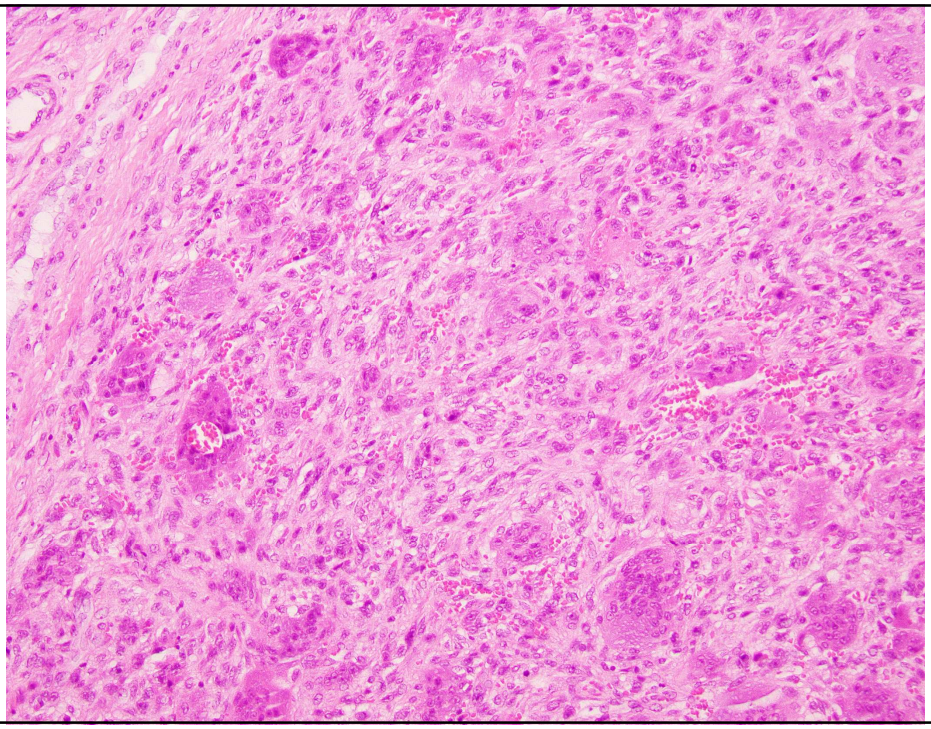
Giant-cell rich spindle cell neoplasm; see NOTE.

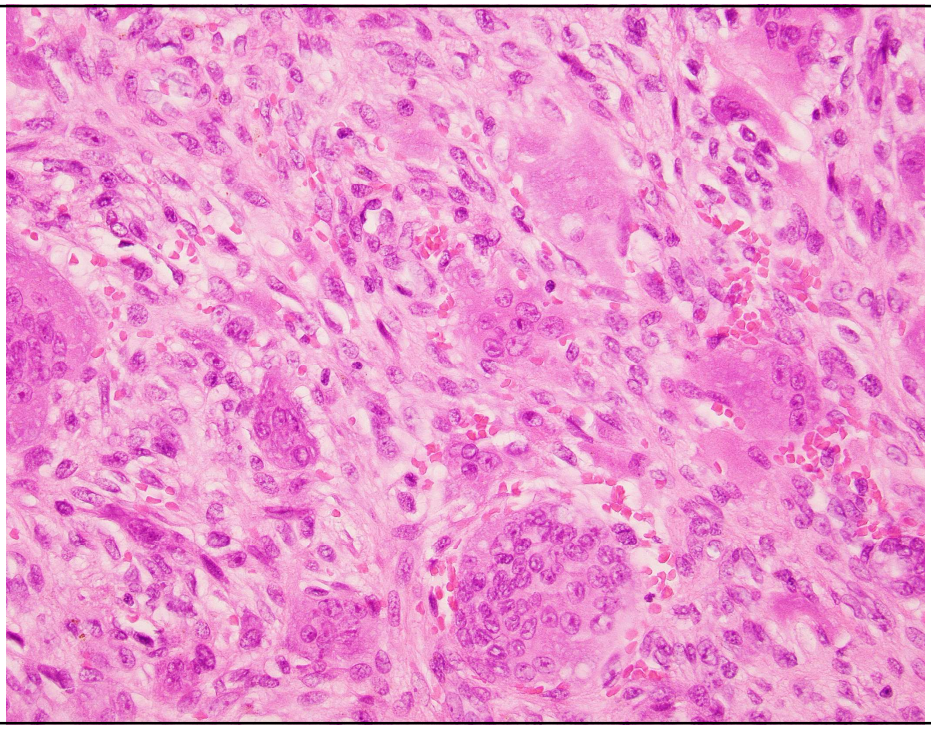
There is no evidence of malignancy.

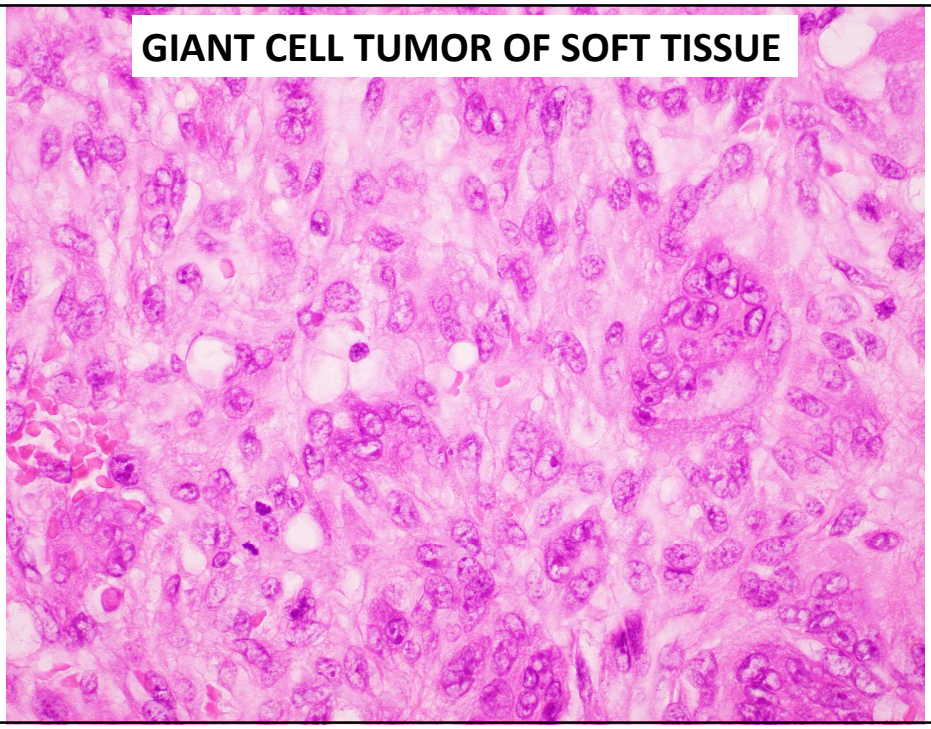
NOTE: In this small biopsy specimen, distinction between giant cell tumor of soft tissue and solid aneurysmal bone cyst is not possible.

- No practical ancillary tests available
- Resection indicated for all entities in DDX

Tumor Type	Molecular Hallmark
Tenosynovial giant cell tumor	*CSF1* fusions
Nodular fasciitis	*USP6* fusions
Giant cell tumor of soft tissue	None (currently)
Aneurysmal bone cyst	*USP6* fusions





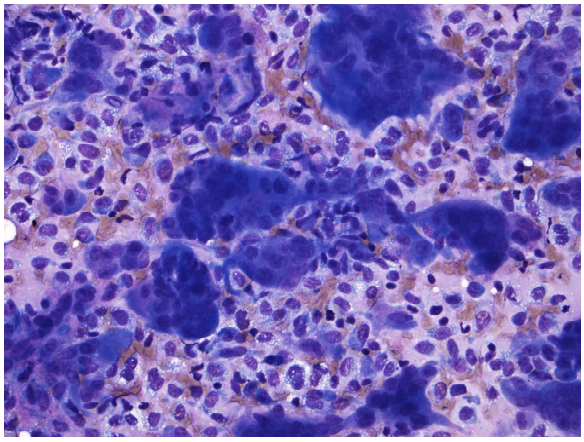

GIANT CELL TUMOR OF SOFT TISSUE

Giant Cell Tumor of Soft Tissue

- Most common during adulthood (5th decade), but can affect patients at any age
- Typically arise in upper and lower limbs
  - Most are superficial (70%); 30% arise deep to fascia
  - Less commonly in trunk (20%) and H&N (7%)
- Broad size range (<1.0 cm to 10.0 cm)
- Tumors are often painless
- Associated with local recurrence (12%), metastases and malignant examples rare
- No definitive IHC or molecular genetic features to date

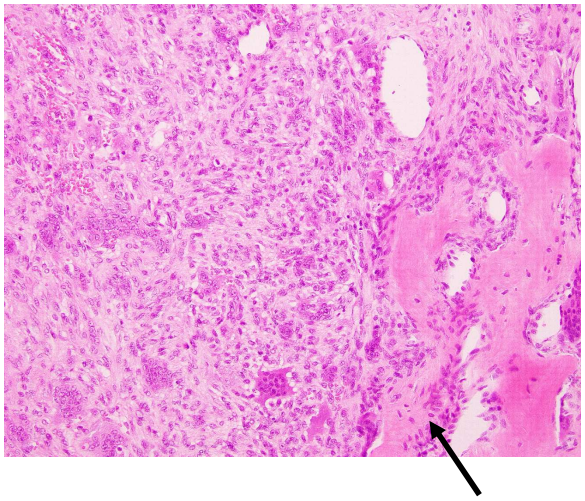
Giant Cell Tumor of ST: Cytologic Features

- Smears generally highly cellular
- Loosely dispersed polygonal, round, or ovoid mononuclear cells and numerous osteoclast-like giant cells, bland uniform nuclei
- Clusters with fibroblast-like spindled cells
  - Giant cells embedded or at edge of clusters
- Osteoclast-like giant cells tend to be very large and bizarrely shaped, often >20 nuclei
- Mitotic activity common
- No osteoid matrix or necrosis



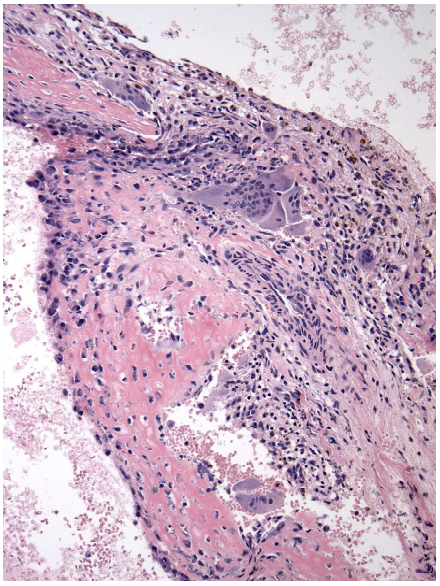
Giant Cell Tumor of ST: Histologic Features

- Definitive dx usually made on resection
- Multinodular growth with fibrous septa and rich fibrovascular stroma
- Distinctive giant cell population is dispersed uniformly throughout
- 50% show metaplastic bone, usually at the periphery (can be seen on imaging; not often sampled on FNAå)

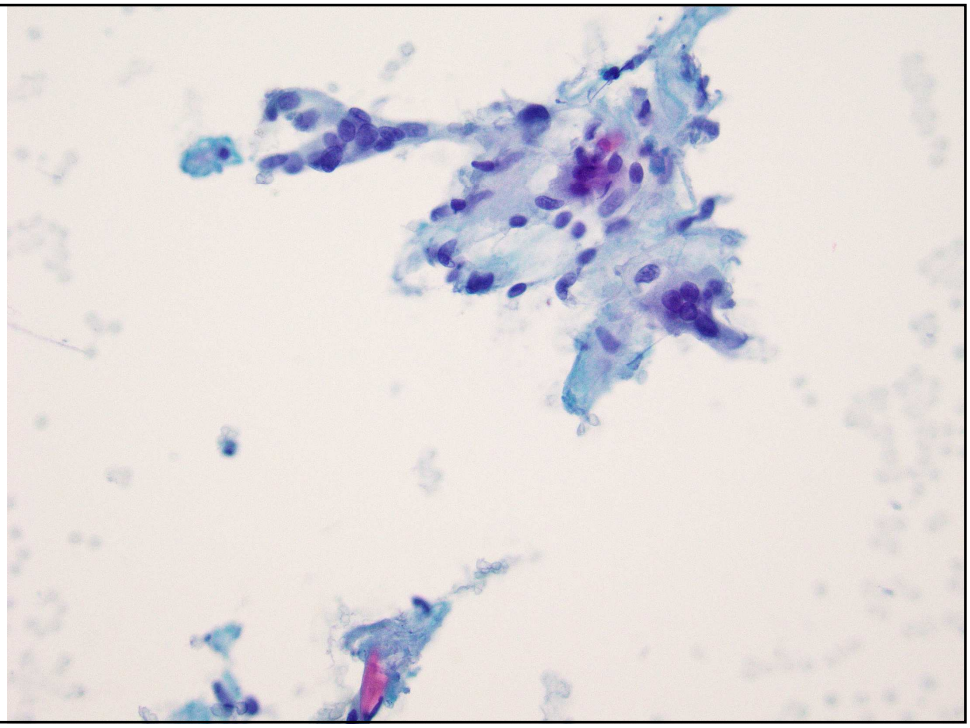


Aneurysmal Bone Cyst

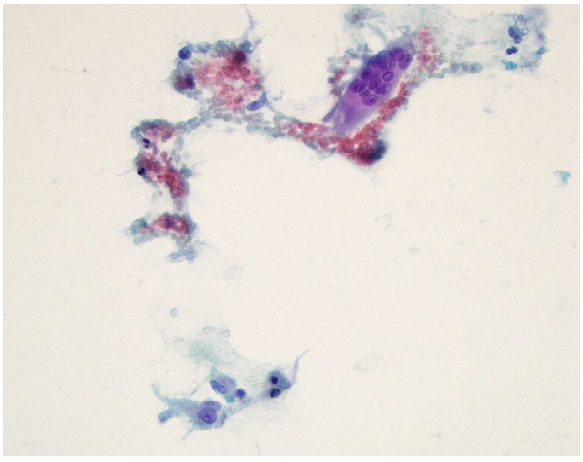
- Can arise in any bone and soft tissue sites
- Common in younger patients (< 20 y)
- Radiology: multicystic with fluid-filled levels and fibrous septa (unless solid)
  - Bone: well-defined, lytic, expansile lesion; thin shell of reactive bone
- *CDH11::USPS* (*USPS* FISH available in some labs)
- Fibrous septa with woven bone, where the osteoclast-like giant cells cluster

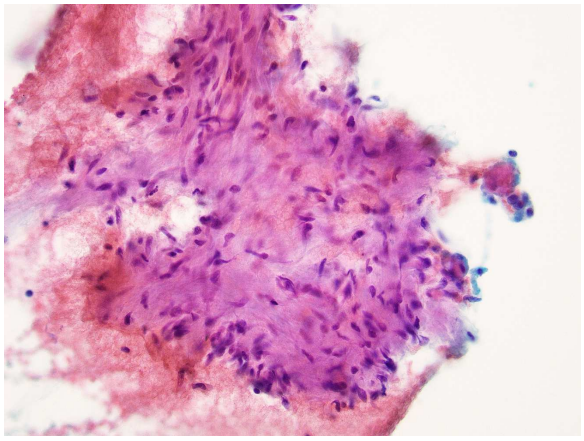


- Smears often hypocellular and bloody
- Spindled myofibroblasts, single and loose fragments
- Osteoclast-like giant cells
- Woven bone often not sampled
- Cannot see cystic blood-filled spaces
- Hemosiderin-laden macrophages

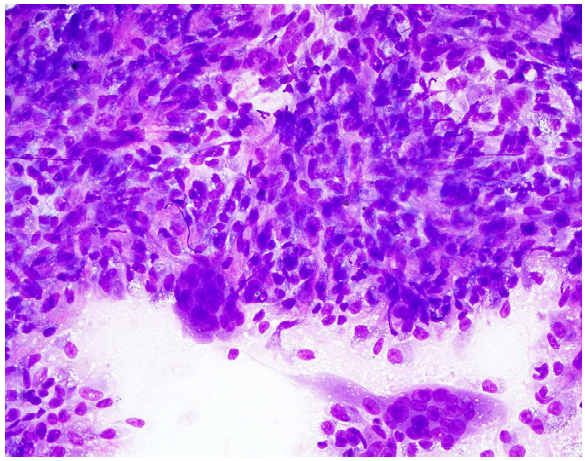


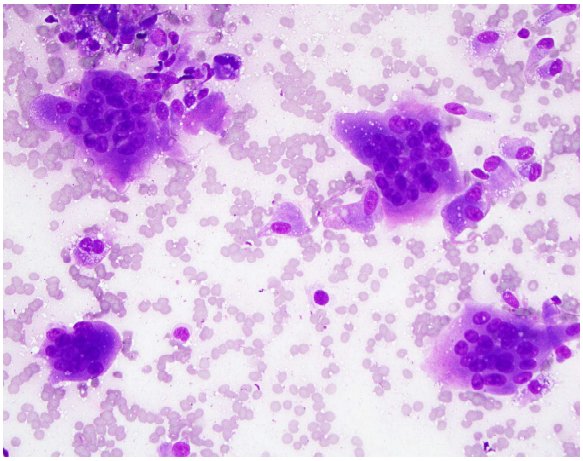
Aneurysmal Bone Cyst





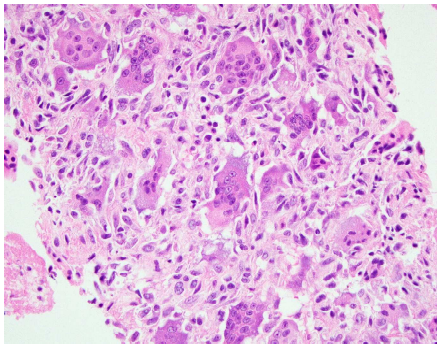
Giant Cell Tumor of Bone

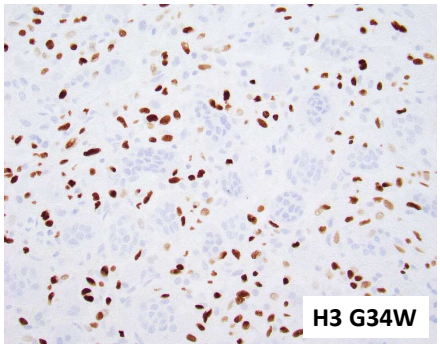




Giant Cell Tumor of Bone

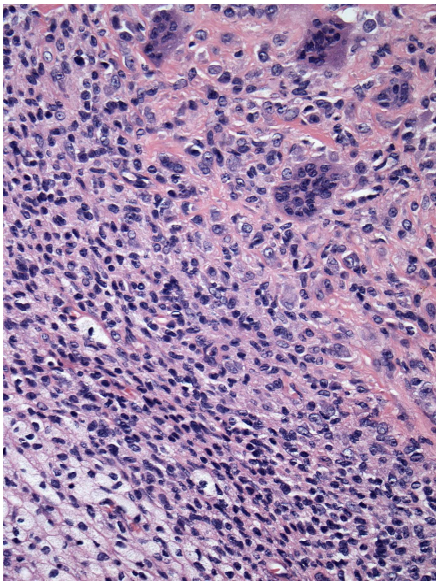
- Arises at the ends of long bones, usually in skeletally mature young adults
- Radiology: Lytic, sharply defined
- Similar morphologic features to giant cell tumor of ST, but molecularly distinct
- *H3F3A* mutations (p.Gly34Trp)
  - H3 G34W IHC is diagnostic (nuclear staining)



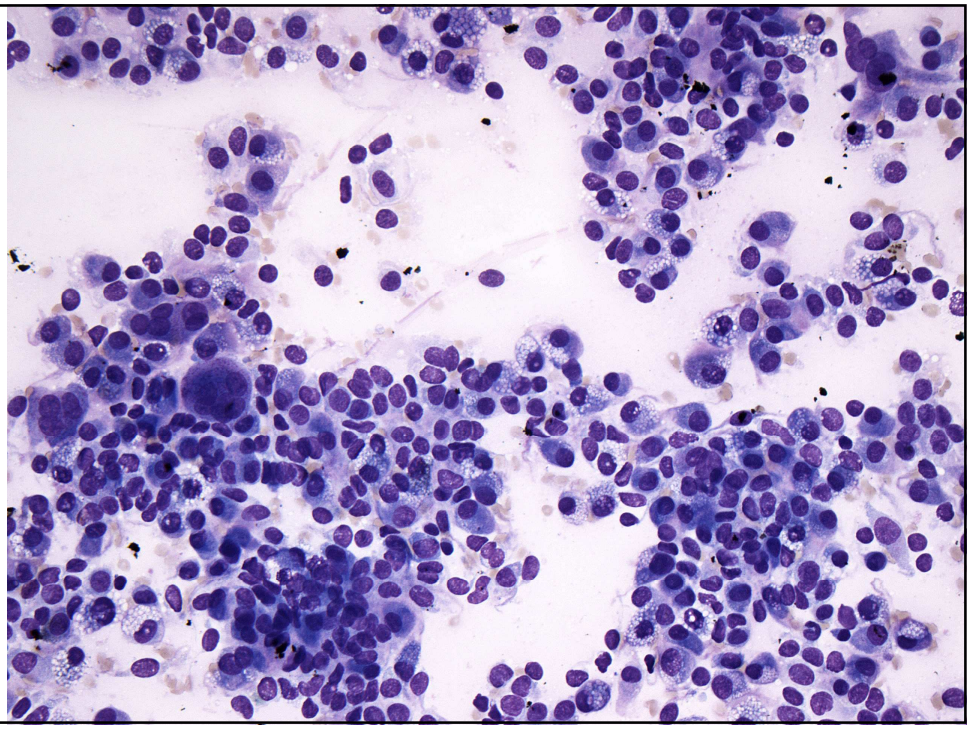


Tenosynovial Giant Cell Tumor

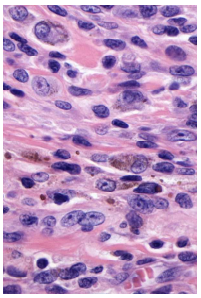
- Adults, slight F>M
- Most common on the extremities and hands
  - Can be intra-articular or extra-articular
- Classified as *localized* (single nodule) and *diffuse* (infiltrative growth, multiple nodules)
- Translocations involving the *CSF1* on chr 1
- IHC: clusterin, desmin

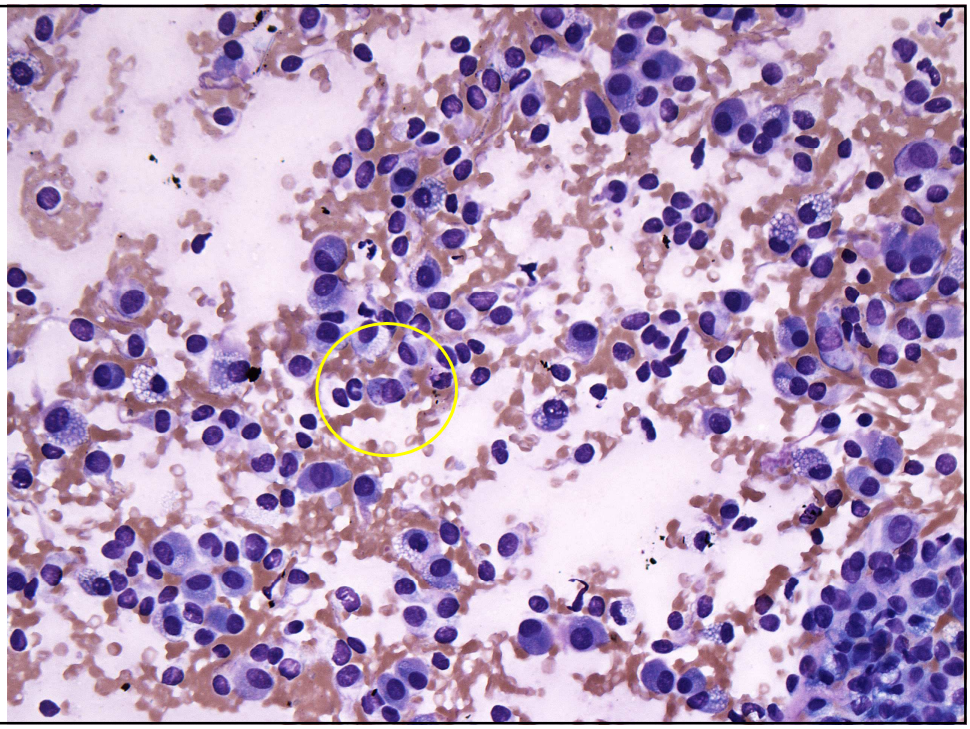


- Admixture of histiocytoid cells, foamy histiocytes, and uniform osteoclast-like giant cells
- Mononuclear cells variably ovoid, spindle, polygonal



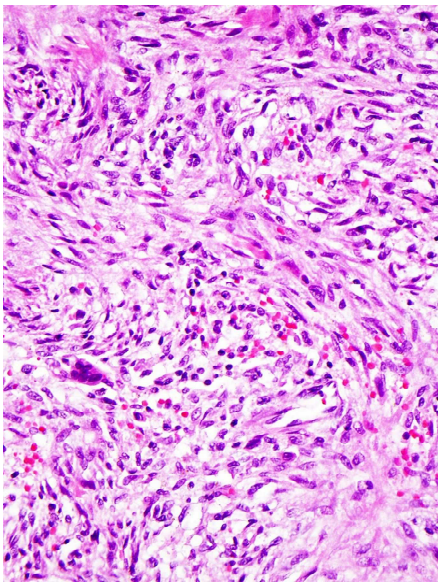
- Hemosiderin (intra- and extra-cellular)
  - "Ladybird cells"



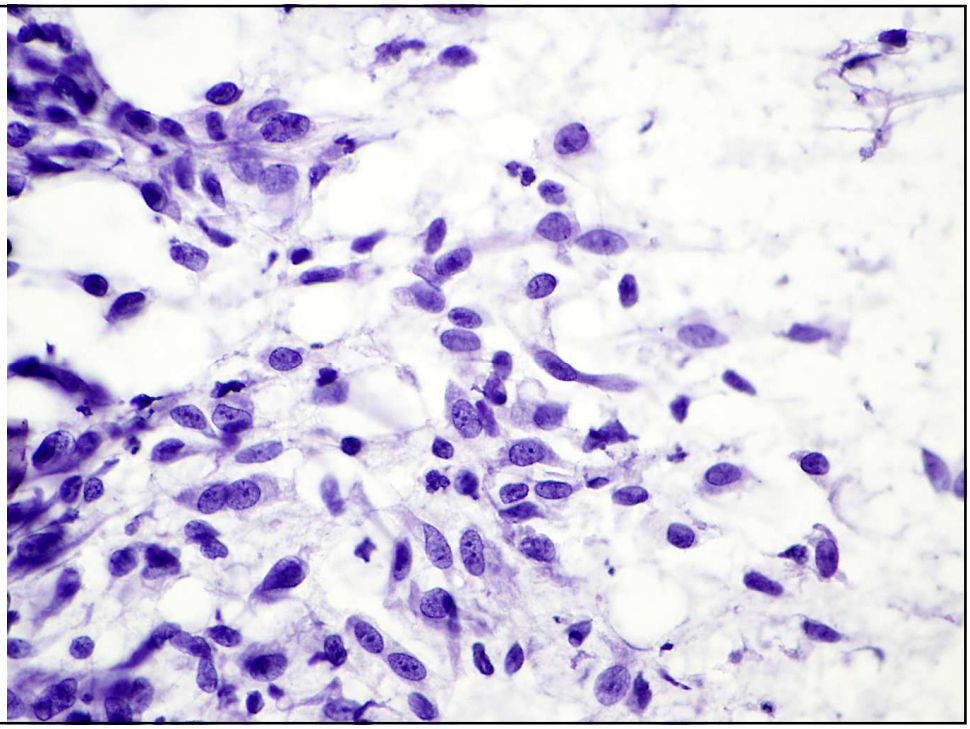


Nodular Fasciitis

- Commonly arise in adulthood (20-40 years)
- Superficial tissues of upper limb, chest and trunk, H&N
  - Small lesions, rarely <5.0 cm
- Characteristic presentation: rapid growth of a painful and tender nodule (1-3 months) then spontaneous regression
- Benign myofibroblasts (tissue culture-like); osteoclast-like giant cells are usually sparse
- *USP6::MYH9*
- No specific immunophenotype: can be positive for SMA

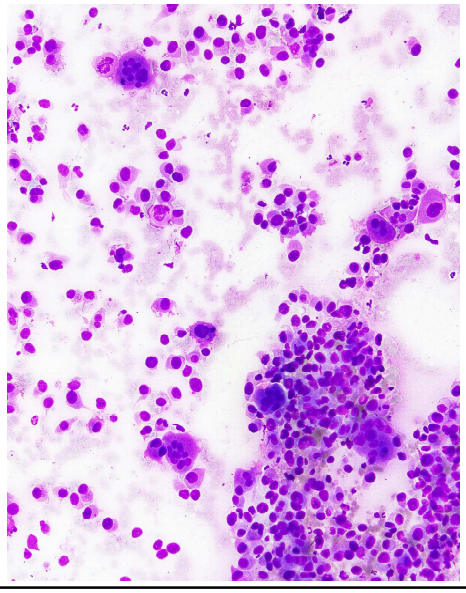


- Spindle and stellate myofibroblasts, single and loosely cohesive fragments
- Bland nuclei, small nucleoli
- Cytoplasm either plump and protruding or wispy and tapering
  - Occasional ganglion-like cells

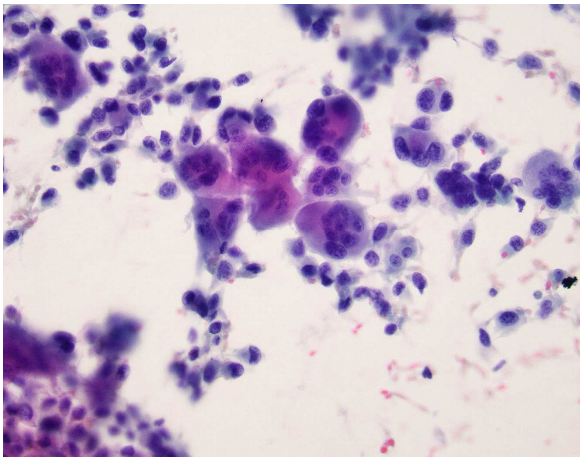


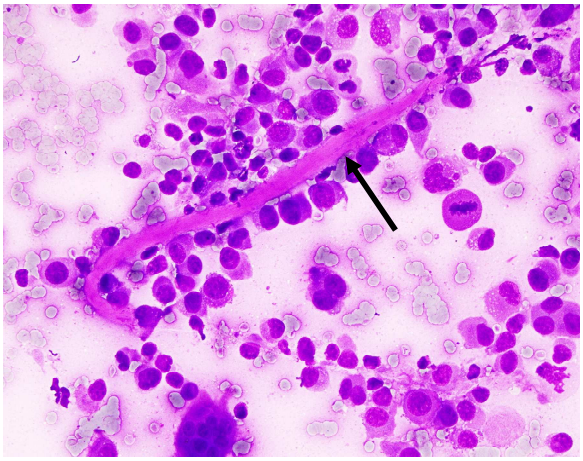
Giant Cell-Rich Extraskeletal Osteosarcoma

- Extraskeletal osteosarcoma is rare (<1% of all soft tissue sarcomas and <6% of osteosarcomas)
- Arise in later adulthood, M>F
- Most cases arise in the lower limbs
- 10% report prior history of trauma or radiation
- Diagnostic feature: neoplastic osteoid matrix produced by malignant, pleomorphic cells
- SATB2 IHC is a marker for osteoblastic differentiation (but does not distinguish malignant vs benign)



Giant Cell-Rich Extraskeletal Osteosarcoma





Osteoid matrix: fibrillary or strand-like; glassy and homogeneous texture with sharp borders

Summary

- For small biopsies of giant cell-rich neoplasms, the most clinically relevant task is identifying malignant processes
  - Correlation with clinical and radiographic data
  - Attention to pronounced atypia, pleomorphism, atypical mitotic figures, osteoid matrix, necrosis
- Definitive classification often not possible– descriptive diagnosis ("giant cell-rich neoplasm") suffices in most scenarios
  - Overlap between giant cell tumor of ST, solid aneurysmal bone cyst, giant cell tumor of bone
  - On cytologic preparations, cannot assess discriminating architectural features (distribution of giant cells and bone; cystic spaces)
  - Ancillary testing can be helpful if available: *USP6* FISH for ABC; H3 G34W IHC for GCT of bone

Microscopy Virtual Session

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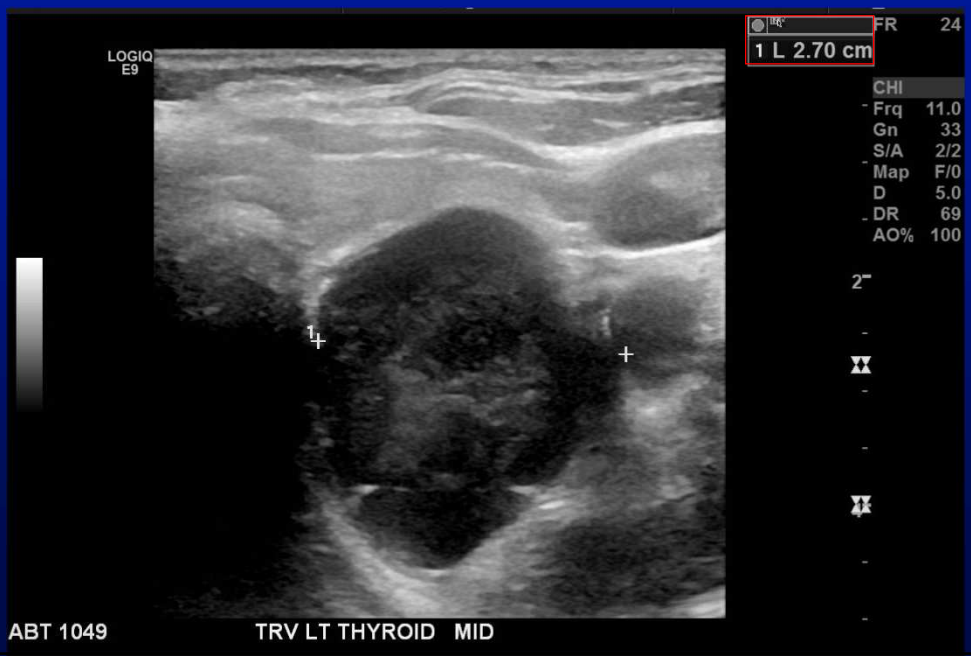
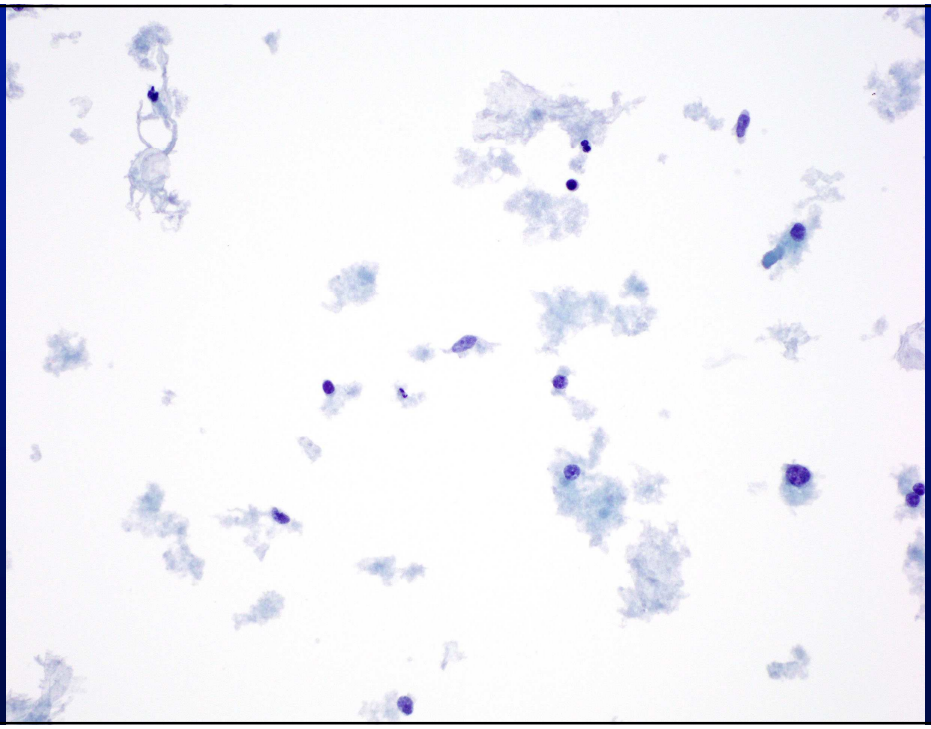
06/12/2023

77-year-old female with bilateral thyroid nodules; left thyroid nodule 2





Diagnosis

1. Benign
2. AUS
3. Suspicious for malignancy
4. Suspicious for follicular neoplasm, oncocytic type
5. Malignant

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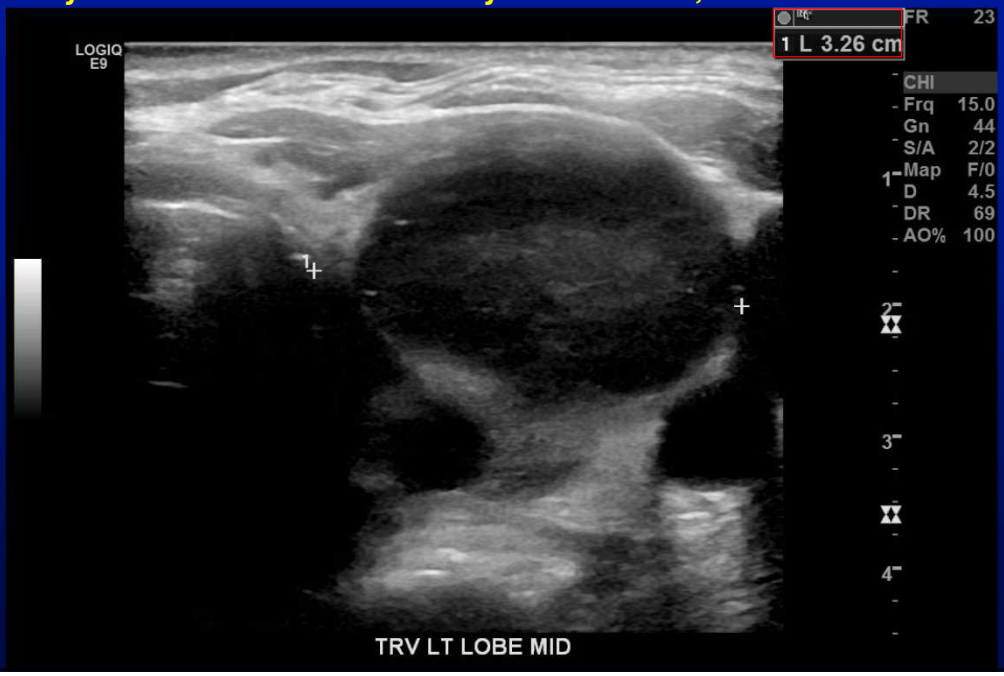
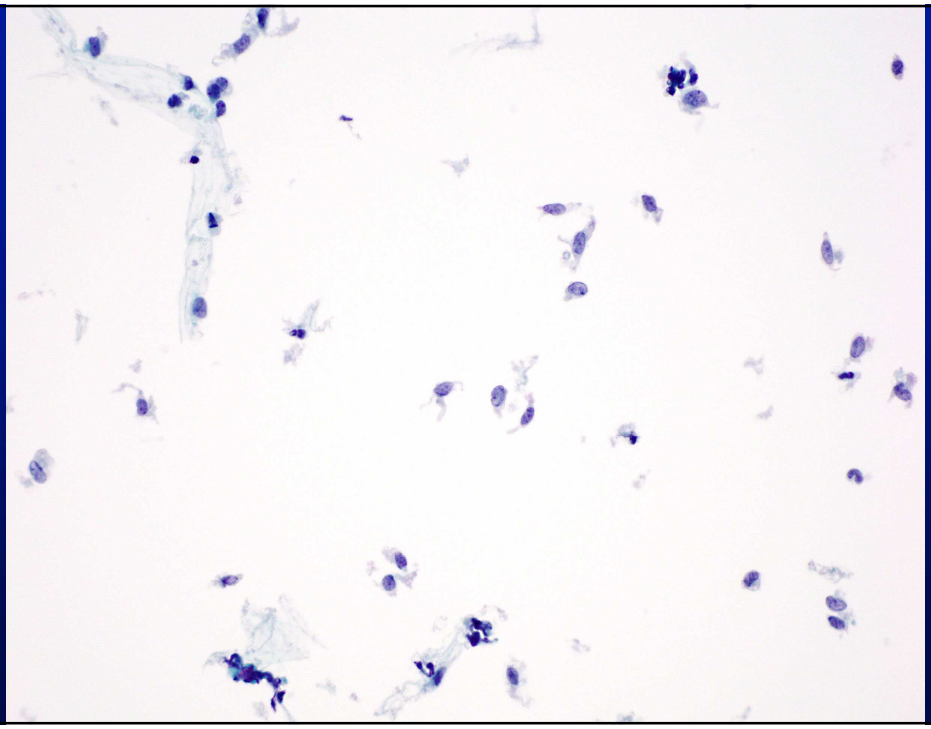
BENIGN.

Benign-appearing follicular cells, colloid, and occasional Hürthle cells, consistent with a benign follicular nodule.
Lymphocytes and lymphohistiocytic aggregates, suggestive of thyroiditis.

77-year female with bilateral thyroid nodules; increase in size





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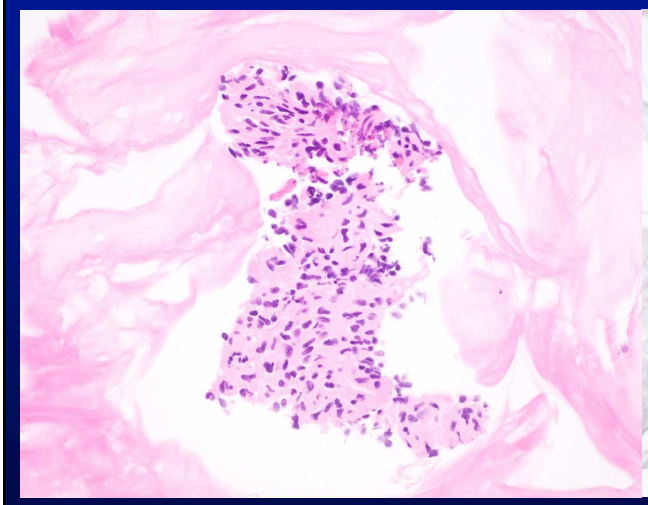
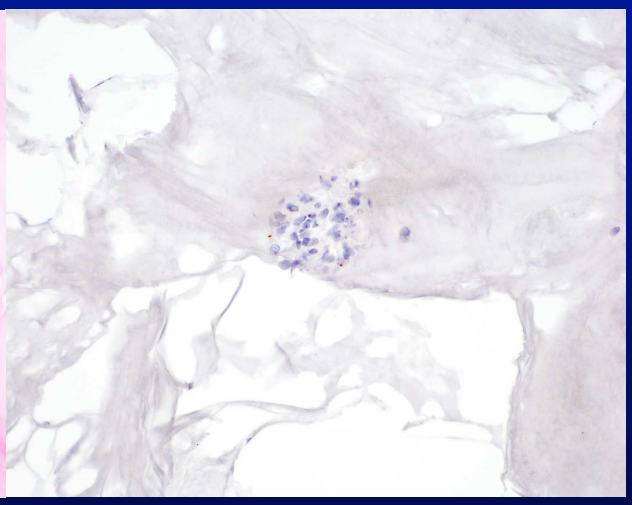
History

1. Posterior fossa tumor: ANAPLASTIC HEMANGIOPERICYTOMA/SOLITARY FIBROUS TUMOR, W.H.O. Grade III in 2015
2. Mets to liver in 2015 s/p partial resection in 2019
3. Mets to lymph node, bone, and peritoneum

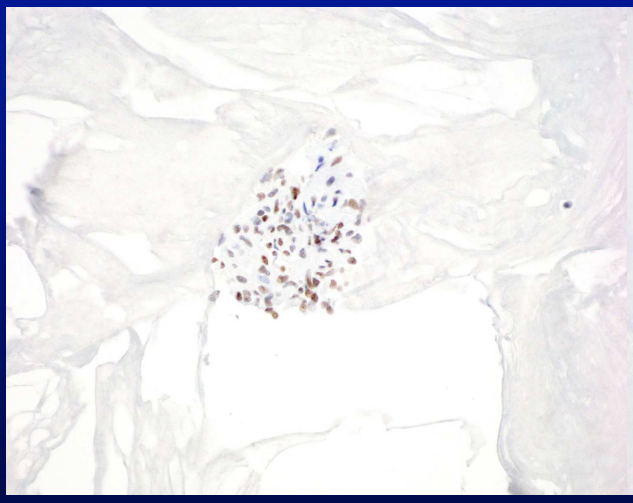
Work-up?

1. Cell block
2. IHCs
   - STAT6
   - CD1a
   - Langerin

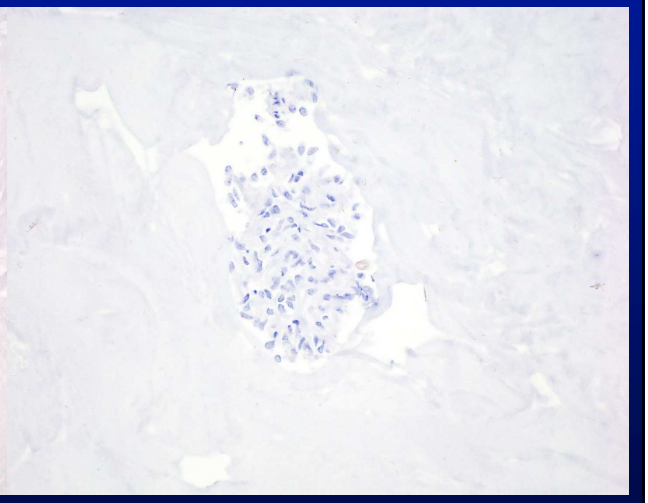




Langerin



STAT6



CD1a

Diagnosis

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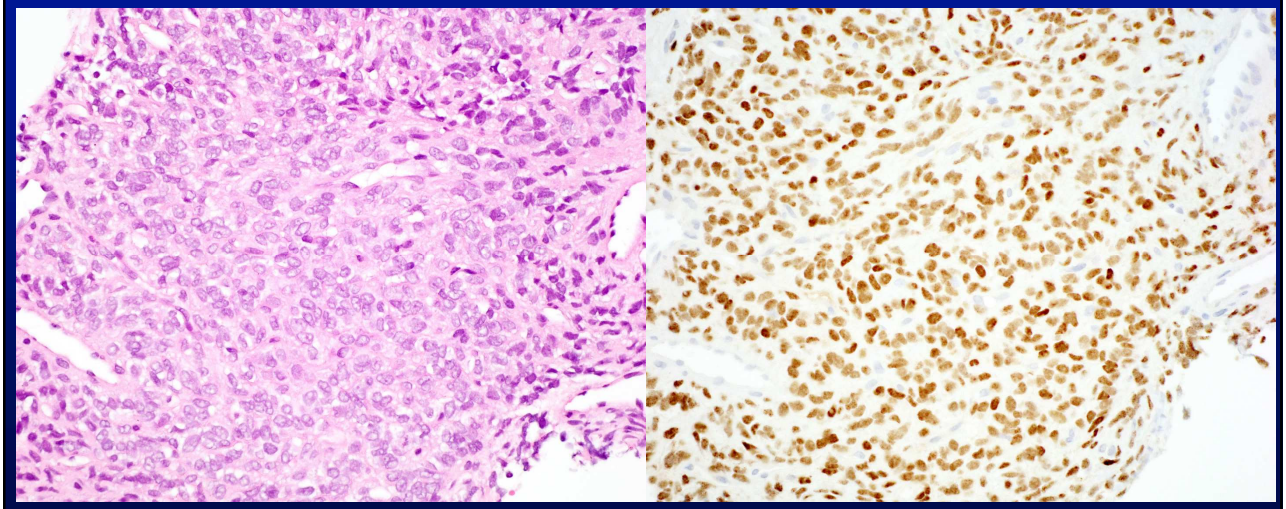
MALIGNANT.
DIAGNOSIS:
Metastatic malignant solitary fibrous tumor.
Immunohistochemistry performed at BWH demonstrates the following staining profile in lesional cells:
Positive: STAT6
Negative: CD1a, Langerin

Gastrohepatic Lymph Node Core Biopsy from 2020



STAT6

Metastatic tumors

1. 0.1~0.3% of thyroid aspirates

2. The first manifestation of an occult malignancy in 25~30% of cases

3. Mets to thyroid:
- Lung cancer vs anaplastic/squamous cell carcinoma of thyroid (thyroglobulin, PAX8, Napsin A)
- Clear cell carcinoma of the kidney vs follicular or Hurthle cell neoplasm (thyroglobulin, TTF-1)
- Melanoma vs medullary thyroid carcinoma (S100, SOX10, TTF-1, calcitonin)
- Lymphoma (LCA, CD3, CD20)

Differential Diagnosis of Primary Solitary Fibrous Tumor in Thyroid

Epithelial neoplasms of thyroid

- Follicular adenoma/carcinoma, PTC: keratin, thyroglobulin, TTF-1
- Papillary carcinoma with desmoid fibromatosis: beta-catenin
- Undifferentiated thyroid carcinoma: clinically rapidly enlarging neck mass; EMA, PAX8
- Medullary thyroid carcinoma: keratin, calcitonin, neuroendocrine markers
- Spindle epithelial tumor with thymus-like differentiation (SET-TLE): children, adolescents, and young patients; keratin+, CD34-, STAT6-

Thompson, LD et al, Head and Neck Pathology (2019) 13:597-605

Differential Diagnosis of Primary Solitary Fibrous Tumor in Thyroid

Spindle cell mesenchymal neoplasms of thyroid

- Smooth muscle tumors: exceedingly rare; leiomyosarcoma (positive: SMA/desmin; negative: CD34/STAT6)
- Peripheral nerve sheath tumor: schwannoma more common; neurofibroma; malignant peripheral nerve sheath tumor (S100, SOX10)
- Synovial sarcoma: keratin, SSX, SS18

Thompson, LD et al, Head and Neck Pathology (2019) 13:597-605

Differential Diagnosis of Solitary Fibrous Tumor

- Spindle cell thymoma: Bcl2 (membranous); TdT, CD1a, CD99
- Cellular schwannoma: S100, SOX10
- Monophasic synovial sarcoma: SSX-18, SSX
- Malignant peripheral nerve sheath tumor: S100, SOX10, H3k27me3
- Spindle cell/desmoplastic mesothelioma: WT1, CK5/6, Calretinin
- Spindle cell melanoma: S100, SOX10, HMB45, PRAME
- Spindle cell/poorly differentiated carcinoma: keratin
- Dedifferentiated liposarcoma: MDM2, CDK4, HMGA2

Lessons Learned

- Complete and thorough medical history
- Be aware of the uncommon entities in thyroid
- Consider metastasis in an unusual thyroid aspirate

Thank you!