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Paul E. Wakely, Jr., MD
# EUS guided FNA, Mediastinum

<table>
<thead>
<tr>
<th>Source</th>
<th>No.</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
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<td>Eur J Cancer 2004;40:559</td>
<td>20</td>
<td>69</td>
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<td>Thorax. 2002;5:98.</td>
<td>79</td>
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<td>Am J Gastroenterol. 2004;99:628.</td>
<td>103</td>
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<tr>
<td>Cancer Cytopathol 2006; 108:206.</td>
<td>155</td>
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</table>

* pts. with NSCLC without enlarged mediastinal lymph nodes by CT

mediastinal/ celiac nodes
Mediastinal FNA

variety of tissue types

♦ epithelial
♦ mesenchymal
♦ lymphoid
♦ germ cell
♦ neural/neuroectodermal
Approaches to Mediastinal Cytopathology – your colleagues

- EBUS-guided FNA: pulmonologist/surgeon
- EUS-guided FNA: gastroenterologist
- percutaneous CT-guided FNA: radiologist
- transbronchial FNA (Wang): pulmonologist/surgeon
Anterior/AnteroSuperior Mediastinum

- thyroid
  - hyperplasia/neoplasm

- parathyroid
  - cyst/neoplasm

- thymic lesions
  - thymoma
  - thymic carcinoma
  - thymic cysts

- lymphomas
  - NHL
  - Hodgkin lymphoma

- germ cell tumors

- paraganglioma
Mediastinal Cysts

• often incidental; asymptomatic
• requires correlation with imaging

• congenital
  – bronchogenic, esophageal, enteric, mesothelial, thymic, parathyroid

• acquired
  – thoracic duct, lymphangioma
Mediastinal Cysts

• **thymic** (unilocular/multilocular)
  – squames, ± lymphocytes, cholesterol crystals, debris

• **mesothelial** (pericardial)
  – acellular, macrophages, ± mesothelial cells

• **foregut** [bronchogenic, esophageal, gastro-enteric]
  – columnar cells (± ciliated), squames, mucoid material, debris

* all cysts can be secondarily inflamed
* several neoplasms may undergo cystic change
pericardial cyst
bronchogenic cyst
cholesterol crystals
Thymoma

• most common 1° mediastinal neoplasm
• anterio-superior mediastinum; middle age
• cytopathology:
  – mixture of epithelial cells & lymphocytes
  – former in clusters or single cells
  – epithelial cells: cytologically bland, rounded or spindle, indistinct nucleoli, poorly defined cytoplasm, blend with lymphocytes
  – potentially mistaken for dendritic cells or histiocytes
Thymoma, WHO type B1
Reactive Lymph Node

Thymoma, WHO Type B1
Reasons for Difficulty in FNA Dx of Thymoma

• proper and adequate sampling is extremely important
  – highly dependent on the technical skill of the interventional radiologist

• helpful histologic features that are not discernible on smears:
  – organotypical differentiation
  – lobule formation
  – dilated perivascular spaces (or marked cystic transformation)
  – capsular invasion

• difficult to distinguish epithelial cells without a cytokeratin stain
FNA & Thymoma Classification

• no reliable correlation of FNA cytology of thymoma with any of the specific histologic subtypes as delineated by the WHO classification

• it is not infrequent for there to be histopathologic transitions in thymoma (mixture of B1, AB, B2, and B3 subtypes) even within the same mass

Suster S, Moran CM. On the histologic heterogeneity of thymic epithelial neoplasms. Impact of sampling in subtyping and classification of thymomas. AJCP 2000;114:760-6
Cytologic Imitators of Thymoma

- Dendritic-lymphocytic aggregates
- Lymphoproliferative Neoplasm
- Spindle cell mesenchymal tumor
- Spindle cell NEC, i.e. Carcinoid
Thymic Carcinoma

- Squamous Cell CA
- Adenocarcinoma
- Basaloid CA
- Clear Cell CA
- Mucoepidermoid CA

- Lymphoepithelioma-like CA
- Sarcomatoid CA
- CA with adenoid cystic CA-like features
- Carcinoma with t(15;19)

*Before you ascribe any of these carcinomas to the thymus, make sure they are not of lung origin.
Thymic Carcinoma

- Carcinoma
  - Squamous Cell Carcinoma; Basaloid CA; Clear Cell CA; Mucoepidermoid CA; Lymphoepithelioma-Like CA; Sarcomatoid CA

- Neuroendocrine CA
  - w-d neuroendocrine CA [Carcinoid Tumor]
  - moderately-differentiated NEC [Atypical Carcinoid]
  - p-d Small Cell NEC
  - p-d Large Cell NEC
w-d NEC, “Carcinoid Tumor”
case

- 71 y/o man with progressive vocal cord paralysis
- imaging: 2.4 cm. enlarged anterior mediastinal mass
- suspect malignancy
- no lab values; no relevant history
- EUS-guided FNA performed
immunostain results

**positive**
- CK AE1/3 (diffuse)
- RCC (focal)
- chromogranin (focal)
- synaptophysin (focal)
- PAS

**negative**
- PAX-2, PAX-8
- calcitonin
- mammaglobin
- CD56
- S-100
- TTF-1/thyroglobin
- p63, cytokeratin 5/6
- PAS-D
initial FNA Dx

Epithelial Lesion, Suspicious For Parathyroid Tissue/Neoplasm

- unstained slides sent for additional testing
GATA3

• GATA = family of transcription factors

• 2 subgroups
  • GATA1,-2,-3 assoc. with CNS/hematopoietic development
  • GATA4,-5,-6 assoc. with endo -, mesoderm derived organs

• GATA3
  – + normal tissues: T-cells, breast, PTH glands, urothelium, distal renal tubules
  – negative normal tissues: lung, parotid, GI tract, thyroid, prostate
  – application: primarily for urothelial, breast neoplasms

Correspondence

GATA3 shows differential immunohistochemical expression across thyroid and parathyroid lesions

DOI: 10.1111/his.12388

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<tr>
<th>Parathyroid</th>
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<td>Parathyroid hyperplasia*</td>
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<td>35 (one weak diffuse)</td>
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<tr>
<td>Atypical adenoma</td>
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<tr>
<td>Parathyroid carcinoma</td>
<td>6</td>
<td>6 (one focal weak)</td>
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*Including one case of recurrent hyperplasia following autotransplantation to the arm.

Histopathology, 65, 288–291.
FINAL DIAGNOSIS

Mediastinal Parathyroid Adenoma
Hodgkin Lymphoma

- **most common mediastinal lymphoma**
- female predominance
- 2\textsuperscript{nd} – 4\textsuperscript{th} decade
- cytopathology:
  - heterogenous lymphocyte background
  - randomly dispersed R-S cells
    - large cells [\(>20 \text{ µm}\)] smooth, multilobated nuclei
    - bi – or uninucleated nuclei
    - enlarged, often misshapen nucleoli
  - pale cytoplasm
  - may undergo cystic change
suppurative HL
Cytologic Mimickers of R-S Cells

- Immunoblasts
- Megakaryocytes
- Dendritic Cells
- Reactive Mesothelial Cells
- Malignant Melanoma
- Large Cell ML (ALCL)

- Large Cell Carcinoma
- Plasmablasts (Myeloma)
- Sarcomas With Epithelioid Features
plasma cell myeloma
peripheral T-cell lymphoma
melanoma
WHO Classification – B Cell Neoplasms

Precursor B-cell neoplasm
  Precursor B lymphoblastic leukaemia/lymphoma

Mature B-cell neoplasms
  CLL/small lymphocytic lymphoma
  Lymphoplasmacytic lymphoma
  Splenic marginal zone lymphoma
  Extranodal marginal zone B-cell lymphoma (MALT)
  Nodal marginal zone lymphoma
  Follicular lymphoma
  Mantle cell lymphoma
  Diffuse large B-cell lymphoma
  Mediastinal(thymic) large B-cell lymphoma
  Intravascular large B-cell lymphoma
  Primary effusion lymphoma
  Burkitt lymphoma/leukaemia
Primary Mediastinal (thymic) Large B-Cell Lymphoma

- 2-3% of NHL
- young adults, 3rd-4th decade; F:M, 2:1
- anterosuperior mediastinal mass
  - often >10 cm.; ± SVC syndrome
  - absent distant nodal or b. marrow involvement
- cytopathology
  - monotonous large lymphocytes
  - visible nucleoli, variable cytoplasm
  - fibrous tissue → hypocellularity, distortion
- IHC: pan B-cell Ag’s, MUM1/IRF4, CD23, PDL2, CD200
Immunophenotyping is mandatory for the definitive cytopathologic diagnosis and subtyping of most NHL.
primary mediastinal large B-cell NHL
Fibrotic Mediastinal Lesions

• Diffuse Large B-Cell Lymphoma
• Hodgkin Lymphoma
• Thymoma
• Solitary Fibrous Tumor
• Inflammatory Myofibroblastic Tumor
• Non-Neoplastic Lesions
• “Our experience demonstrates that FNA cytology of primary mediastinal DLBL with sclerosis can be challenging, with a potential for a false-negative diagnosis due to limited cellularity secondary to the sclerosis or a misdiagnosis as a spindle cell neoplasm due to distortion of these cells by the fibrous matrix.”

Lymphoblastic Lymphoma

- 30-45% pediatric lymphomas
- adolescents and young adults
- 80% - anterior mediastinal mass; SMS
- cytopathology
  - uniform population of blasts
  - $L_1$ and $L_2$ morphology
  - TBMs, mitoses variable
- 85% T-cell
- pitfall: cortical thymic lymphocytes
Superior Mediastinal Syndrome

**Definition**

- SVC compression/obstruction
- tracheal compression/respiratory symptoms
- signs and symptoms
  - cough/ hoarseness/ dyspnea/ wheezing/ cyanosis/orthopneoa/ syncope
lymphoblastic lymphoma
## Lymphoblastic Lymphoma - accuracy

<table>
<thead>
<tr>
<th>Year/Author/Journal</th>
<th>Spec(%)</th>
<th>Sens(%)</th>
<th># cases</th>
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<td>100</td>
<td>16</td>
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<td>1993 / Tani / <em>Diagn Cytopathol</em></td>
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<td>100</td>
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<td>1992 / Jacobs / <em>Acta Cytol</em></td>
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<td>1987 / Kardos / <em>Cancer</em></td>
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Germ Cell Tumors
Mediastinal Teratoma

- adolescents/ young adults
- anterior mediastinum
- mature teratoma (common, 70%)
  - squames, sebaceous cells
  - hyaline cartilage, adipose tissue
  - goblet cells, ciliated respiratory epithelium
- immature teratoma (1-2% of cases, mostly males)
  - neuroectodermal tissue: malignant small rounded cell tumor
  - malignant mesenchymal components
- pitfall: mixed germ cell tumor
immature teratoma
Mediastinal Germinoma/Seminoma

• 2\textsuperscript{nd} most frequent mediastinal GCT
• almost exclusive to men
• cytopathology:
  – dimorphic population of large & small cells
  – loose groups, single cells
  – macronucleoli, cytoplasmic vacuoles, “tigroid” background, bare nuclei, ± granulomas

• pitfall: mixed germ cell tumor
seminoma
Non-Seminomatous GCT

• Yolk Sac T./ Embryonal CA/ ChorioCA
• clinical features similar to dysgermininoma
• cytopathology:
  – cells in loose or tightly aggregated clusters
  – ± papillary or glandular pattern
  – large cytologically malignant cells
  – cytoplasmic vacuoles
  – ± hyaline globules
• unable to reliably distinguish by FNA smears alone
• pitfall: Non-Small Cell Carcinoma
embryonal CA
yolk sac tumor
yolk sac tumor – PAS stain
IHC – Germ Cell Tumors
(positive staining)

- **Seminoma**
  - CD 117 (c-kit)
  - CAM 5.2 (weak)
  - Cytokeratin AE1/3 (weak)
  - OCT 3/4

- **Non-Seminomatous**
  - Cytokeratin AE1/3
  - CD 30 (embryonal CA)
  - SOX2
  - PLAP
  - β HCG (chorioCA)
  - OCT 3/4
Posterior Mediastinum

- schwannoma
- ganglioneuroma
- MPNST
- paraganglioma

- neuroblastoma
- ganglioneuroblastoma
- neurofibroma
Schwannoma

- most common posterior mediastinal tumor
- 20-40 yrs.
- cytopathology:
  - spindle cell in syncytial clusters & single forms
  - smooth or “wavy / fish-hook” nuclei
  - pale, thin cytoplasmic processes
  - nuclear palisading but Verocay bodies rare
- pitfall: ganglioneuroma
Ganglioneuroma

- posterior mediastinum
- adolescents - young adults; females
- solitary, smooth contoured paraspinal mass
- cytopathology:
  - extremely hypocellular smears
  - microfragments of spindle and ganglion cells
  - ganglion cells: enlarged, abundant cytoplasm, single or dual round nuclei, single nucleolus
- pitfall: differentiating neuroblastoma, PNST
ganglioneuroma
ganglioneuroma
Neuroblastoma and Variants

- posterior mediastinum
- ~15% of all Nbl.; 2/3 of neurogenic mediastinal tumors in children
- birth – 8 years
- cytopathology:
  - hypercellular smears
  - malignant “small” “round” cells
  - variable neuropil [H-W rosettes]
  - ± ganglion cells
- pitfall: other malignant SRCT
neuroblastoma
neuroblastoma
ganglioneuroblastoma
ganglioneuroblastoma