Current Issues in Practical Hematopathology: Thymomas and Mediastinal Lymphomas

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Disclosures
- I have no disclosures relevant to the content of this lecture

Normal thymus components

- Thymic epithelium
  - Derives from common endodermal ‘thymic stem cell’ originating from 3rd pharyngeal pouch
  - Keratin+

- Lymphoid cells
  - Derive from bone marrow precursors
  - Precursor T and NK cells (vast majority)
    - Enter thymus as primitive CD3-/CD4-/CD8- cells
    - Thymic B cells (sparse)

- Dendritic cells, macrophages

- Mesenchymal cells

Normal thymus
Role of pathologist in thymoma management

- Identify tumor as thymoma
  - Tumor arising from thymic epithelium
- Determine presence and degree of invasion (stage)
- Determine histologic subtype
  - WHO Working Group Classification 2004, as modified from original classification of 1999
Types of invasion*

- Fully encapsulated (T1, Masaoka I)
- Minimally invasive (T2, Masaoka II)
  - *Penetrates* capsule to invade pericapsular connective tissue, fat, or adjacent thymus
- Invades other organs (lung, pleura, pericardium, diaphragm, chest wall) (T3, Masaoka III)

*TNM Classification and Modified Masaoka Staging systems*
### WHO Thymoma Classification

<table>
<thead>
<tr>
<th>WHO</th>
<th>Features</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type A</td>
<td>Spindle cell morphology, medullary-type lymphocytes</td>
<td>Good</td>
</tr>
<tr>
<td>Type B1</td>
<td>Recapitulation of normal thymic architecture ('organoid')</td>
<td>Good</td>
</tr>
<tr>
<td>Type B2</td>
<td>Epithelial cells frequent, cortical-type lymphocytes</td>
<td>Fair</td>
</tr>
<tr>
<td>Type B3</td>
<td>Atypical epithelial cells predominate</td>
<td>Fair to poor</td>
</tr>
<tr>
<td>Type AB</td>
<td>Mixed features (usually A + B1)</td>
<td>Good</td>
</tr>
<tr>
<td>‘Type C’</td>
<td>Carcinoma</td>
<td>Poor</td>
</tr>
</tbody>
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#### Thymoma Type A

- Well-circumscribed
  - Mean size 10 cm
  - 80% T1
- Derive from medullary-type epithelial cells
- Lymphocyte-poor
  - Lymphocytes mostly have phenotype of medullary thymocytes (TdT-, CD1a-)
- Excellent prognosis, ‘benign thymoma’

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**Thymoma: Stage and Type do make a difference. . .**

Thymoma Type A

Key features of Type A:
- Bland-appearing ovoid to spindled cells
- Absence of mitotic figures
- Sparse lymphocytes in most areas
- Epithelial cells may express CD20

Thymoma Type B1

- Well-circumscribed
  - 60% T1, 25% T2
- Derive from ‘common’ thymic epithelial cell
- Lymphocyte-rich
  - Mainly cortical-type, with more mature T cells in medullary areas
- Excellent prognosis
  - Behavior depends on stage and resectability

Thymoma Type B1

Type B1

Cytokeratin
Key features of Type B1:
- Bland-appearing round epithelial cells lost in a sea of cortical thymocytes
- Mitotic figures usually frequent in thymocytes
- Epithelial cells may have small nucleoli
- Scattered pale spots that recapitulate normal thymic medulla
Key features of Type AB:
- Bland-appearing epithelial cells range from round to spindled in discrete areas
- Lymphocyte-rich areas usually resemble B1, not B2 thymomas
- Epithelial cells may express CD20, like Type A thymomas

Features of Thymoma Type B2
- Circumscribed or invasive
  - T1, T2, T3 about equal
  - 10% disseminated
- Derive from cortical-type epithelial cell
- Lymphocytes present, but fewer than B1
  - Immature cortical type
- Intermediate prognosis
Key features of Type B2:
- Epithelial cells more frequent, but many cortical thymocytes are still present
- Tumor cells may have nucleoli and form clusters
- Lack areas of medullary differentiation

Features of Thymoma Type B3
- Infiltrative
  - T3 and T2 common
  - 15% disseminated
- Derive from cortical-type epithelial cell
- Lymphocyte-poor
- Intermediate prognosis
  - Often unresectable
  - Local recurrence frequent
Key features of Type B3:
- Epithelial cells form sheets
- Lymphocytes are sparse
- Epithelial cells are atypical, with 'raisinoid', crinkled, or (less frequently) vesicular nuclei and often distinct cell borders

Spindled cell proliferations in the anterior mediastinum

- **Type A thymoma**
  - Densely cellular, but cytologically bland
  - No or very rare mitotic figures
  - May express CD20

- **Type B3 thymoma**
  - Cells oval, not spindled
  - Nuclear atypia and usually increased mitotic activity

- **Thymic sarcomatoid carcinoma**
  - Overtly malignant cytology, high mitotic rate

- **Solitary fibrous tumor**
  - Keratin-, CD34+, CD99+

Weissferdt A Appl Imn Mol Morphol 2011;19:329
Thymic carcinoma

- Squamous cell
- Basaloid
- Mucoepidermoid
- Lymphoepithelioma-like
- Sarcomatoid/carcinosarcoma
- Clear cell
- Adenocarcinoma
  - Papillary adenocarcinoma
- Neuroendocrine carcinomas
  - Poorly-differentiated (small cell or large cell types)
  - Well-differentiated (thymic carcinoid)
- Carcinoma with t(15;19)
**Thymoma versus thymic carcinoma**

- **‘Benign’ thymoma**
  - Cytologically bland epithelial cells
  - Recapitulate thymic architecture
  - Typically CD5- and CD117-
  - β5t positive
  - Autoimmune associations common

- **Thymic carcinoma**
  - Cytologically malignant epithelial cells
  - Do not resemble normal thymus
  - Often CD5+ and/or CD117+
  - β5t negative
  - No autoimmune associations


**Thymic carcinoma versus other tumors**

- The thymus can be a site of invasion of metastasis from lung or other carcinomas
- Clinical and radiologic features are critical in this distinction
  - No specific keratin expression profile
  - May express calretinin (1/3 of thymic carcinomas)
  - TTF1 negative
- β5t specific for thymic origin, but only expressed in B2/B3, not thymic carcinomas
- CD5 positivity favors thymic origin
  - 40-50% CD5 positive, negative in lung and other carcinomas

Pan CC Hum Pathol 2003; 34:1155; Yamada Y AJSP 2011;35:1296

**Thymic lymphomas**

- Relatively common
  - Mediastinal large B-cell lymphoma (MLBCL)
  - Classical Hodgkin lymphoma (CHL)
  - T-lymphoblastic lymphoma (T-LBL)
- Uncommon
  - Thymic MALT lymphoma
  - Anaplastic large cell lymphoma and other peripheral T/NK lymphomas
  - ‘Grey zone’ lymphoma (DLBCL/CHL overlap)
T-lymphoblastic lymphoma

- Precursor T-cell neoplasm
  - CD3+, TdT+, CD1a+, CD99+, CD4/CD8 variable, keratin-
- Children and young adults (M>F)
- May have associated leukemic involvement with circulating T-lymphoblasts
- Treatment is chemotherapy, not surgery

Pitfalls in distinguishing T-LBL from thymoma

- Thymomas may occur in children and young adults
- Reactive T-lymphocytosis can be associated with thymomas
- Immunophenotype and morphology of T-LBL and lymphocytes of cortical thymomas can be identical

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<thead>
<tr>
<th>T-LBL</th>
<th>Thymoma</th>
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<tbody>
<tr>
<td>Infiltrative</td>
<td>Lobulated</td>
</tr>
<tr>
<td>No or few keratin+ cells</td>
<td>Keratin+ tumor cells</td>
</tr>
<tr>
<td>Clonal TCR rearrangements</td>
<td>Polyclonal T cells</td>
</tr>
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**Mediastinal large B cell lymphoma (MLBCL)**

- Tumor of young adults (F > M)
- Locally aggressive with dissemination to extranodal sites
  - Often very bulky mass, SVC syndrome
- Thought to derive from thymic B-cell
  - Gene expression profiling has shown that MLBCL is distinct from DLBCL and has some similarities to classical Hodgkin lymphoma
- Immunophenotype
  - CD19+, PAX5+, CD20+, CD79a+, CD30 often weak+
  - Ig clonally rearranged, but not expressed
Mediastinal large B-cell lymphoma

Courtesy of Dr. Aliyah Sohani
The molecular signature of MLBCL differs from that of other DLBCL

**Over-expressed**
- MAL, FIG-1
- Fibronectin
- Collagens
- c-REL, TRAF1, STAT1

**Under-expressed**
- IgM
- MHC class II

Nodal DLBCL MLBCL

Savage K et al. Blood 2001; 102:3871
Rodig SJ et al. AJSP 2007; 31:106

Nodular sclerosis classical Hodgkin lymphoma

Classical Hodgkin lymphoma

MLBCL
### B-cell lymphoma, intermediate between DLBCL and CHL ("Grey-zone lymphoma")

- **B-lineage lymphoma with overlapping clinical, morphological and/or immunophenotypic features between CHL and DLBCL, especially PMBL**
- **Most commonly associated with mediastinal disease, but may occur in peripheral lymph nodes**
- **Provisional lymphoma category in 2008 WHO Classification**

### NSCHL versus MLBCL

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<th>NSCHL</th>
<th>MLBCL</th>
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<tr>
<td>Reactive cells (esp eos)</td>
<td>Fewer reactive cells</td>
</tr>
<tr>
<td>Lacunar cells, diagnostic RS cells</td>
<td>Oval or lobated cells, clear cytoplasm</td>
</tr>
<tr>
<td>Fibrous bands</td>
<td>Fine sclerosis</td>
</tr>
<tr>
<td>Necrosis, polys</td>
<td>Necrosis, no polys</td>
</tr>
<tr>
<td>CD20 weak, PAX5 weak</td>
<td>Diffuse strong CD20+ and PAX5+</td>
</tr>
<tr>
<td>CD45-, BCL6-</td>
<td>CD45+, Bcl6+,</td>
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<tr>
<td>CD30 strong, CD15+</td>
<td>CD30+/-, CD15-</td>
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<td>SVC syndrome rare</td>
<td>SVC syndrome may occur</td>
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### Occurrence
- Typically young men (20-40 y)
- Mediastinum, lung, regional nodes, spleen; extranodal sites uncommon
- May occur in patients with a history of or concurrent PMBL or NSCHL

### Outcome:
- Aggressive, worse than CHL or MLBCL
- Optimal clinical management uncertain

Traverse-Glehen AJSP 2005
Pitfalls in the pathologic evaluation of mediastinal tumors

- Real-time evaluation at resection
  - Frozen section assessment
  - Sampling of tumors
- FNA and small biopsy samples
  - Histologic appearance may be misleading
  - Role is to determine chemotherapy (lymphoma) vs surgical resection (others)
  - Important to establish histotype prior to any neo-adjuvant therapy

Frozen section evaluation of mediastinal tumors

- Assure tissue is adequate (if biopsies)
  - If all tissue is crushed, request more!
- Take tissue for ancillary studies if lymphoma is in differential diagnosis
  - Flow cytometry +/- Cytogenetics
- Demonstrate adequate margins if thymoma/thymic carcinoma
- Thoroughly sample all parts of tumor
Survival in thymomas: Resectability and recurrence

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Diagnosis of thymoma on FNA

Neoadjuvant therapy (NAT) and thymomas

- Locally advanced thymomas are often treated prior to resection with NAT
  - Usually a combination of platinum-based chemotherapy and XRT
- NAT affects the histologic appearance of thymoma at the time of resection
  - Extensive necrosis/hyalinization
  - NAT-induced atypia may lead to false diagnosis of carcinoma
How to successfully navigate pre-treated thymomas...

- Obtain the pre-therapy biopsy if possible to compare
- Thoroughly sample resected tumor to find viable/cellular areas
- Beware overcalling cytologic atypia as carcinoma, particularly if only isolated cells
Summary

- The pathologist plays a key role in the clinical management of thymomas
  - Distinction between thymoma versus T-LBL
  - Subtyping and staging of resected tumors
- Classification of thymomas according to WHO provides important prognostic information
- MLBCL and NSCHL are biologically related entities and may overlap

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