Selected Pitfalls in Lymphoma Diagnosis

Things that I consider clinically significant pitfalls

- Benign versus malignant
  - Hyperplasias
  - Benign disorders that mimic lymphoid neoplasms
  - Precursor/in situ lymphoid lesions
- Misclassification of a lymphoid neoplasm:
  - Changes in therapy and/or prognosis
- Misclassification of a lymphoid neoplasm:
  - Hematopoietic versus non-hematopoietic neoplasm

Benign processes possibly mistaken for neoplastic processes

- Benign versus lymphoma
  - Mimics of lymphomas
    - Follicular hyperplasia versus follicular lymphoma
    - Marginal zone hyperplasia versus marginal zone lymphoma
    - Kimura disease
    - Acute EBV/infectious mononucleosis
    - IgG4 lymphadenopathy
    - Kikuchi-Fujimoto disease
    - PTGC versus NLPHL

Benign Lymph Nodes

Hyperplasia of normal components

- Follicular
- Mantle zone/primary follicle
- Marginal zone
- T cell (nodular paracortical)
- Interfollicular/Immunoblastic
- Progressive transformation of germinal centers
- Plasmacytoid dendritic cells
- Other cell types
Marginal zone hyperplasia

- Normal marginal zone:
  - Present in spleen, peri-tonsillar lymph nodes, mesenteric lymph nodes
  - Small lymphocytes with mature chromatin and some clear cytoplasm
  - Monocytoid B-cells
  - Almost always accompanied by neutrophilic (benign or malignant)

- Toxoplasmosis
- CMV lymphadenitis
- HIV/AIDS lymphadenitis
- Other viral adenopathies

- Differential Diagnosis:
  - Marginal zone lymphoma, other lymphomas with "clear cell" differentiation

Distinction of FH from FL

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Follicular Hyperplasia</th>
<th>Follicular Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Architecture</td>
<td>Preserved</td>
<td>Effaced</td>
</tr>
<tr>
<td>Follicle size and shape</td>
<td>Both vary</td>
<td>Little variation</td>
</tr>
<tr>
<td>Follicle density</td>
<td>Normal – increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Follicle polarization</td>
<td>Often seen</td>
<td>Not seen</td>
</tr>
<tr>
<td>Mitotic rate</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Mantle zone</td>
<td>Well-formed</td>
<td>Poorly-formed</td>
</tr>
<tr>
<td>Cell cytology</td>
<td>Variety of cell types</td>
<td>More uniform, abnormal cells</td>
</tr>
<tr>
<td>Tingle-body macrophages</td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>

Marginal Zone Hyperplasia:
- Perifollicular isolation
- Clear cell cytology
Marginal zone hyperplasia

<table>
<thead>
<tr>
<th>Normal marginal zone</th>
<th>MZ Hyperplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present in spleen, periocular lymph nodes, mesenteric lymph nodes</td>
<td>Toxoplasmosis</td>
</tr>
<tr>
<td>Small lymphocytes with mature chromatin and some clear cytoplasm</td>
<td>CMV lymphadenitis</td>
</tr>
<tr>
<td>Monocytoid B-cells</td>
<td>HIV/AIDS lymphadenitis</td>
</tr>
<tr>
<td>Almost always accompanied by neutrophils (benign or malignant)</td>
<td>Other viral adenopathies</td>
</tr>
<tr>
<td></td>
<td>Differential Diagnosis: Marginal zone lymphoma, other lymphoma with &quot;clear cell&quot; differentiation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>MZH</th>
<th>Early MZL</th>
<th>MZL</th>
</tr>
</thead>
<tbody>
<tr>
<td>limited extent</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Follicular colonization</td>
<td>-</td>
<td>-/+</td>
<td>+</td>
</tr>
<tr>
<td>MZ distribution</td>
<td>+</td>
<td>+</td>
<td>+/- (diffuse)</td>
</tr>
<tr>
<td>B-cell network</td>
<td>NL</td>
<td>Abnormal (focal)</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Low Ki-67 in follicles</td>
<td>-</td>
<td>-/+</td>
<td>+</td>
</tr>
<tr>
<td>CD43 expression</td>
<td>No</td>
<td>-/+</td>
<td>-/+</td>
</tr>
</tbody>
</table>

Marginal Zone Lymphoma and follicular colonization

- Follicular colonization can make follicles appear abnormal
- Other times, the abnormalities can only be seen by immunohistochemistry
- Marginal zone lymphoma cells have a propensity to invade or colonize non-neoplastic follicles
- These then are composed of an admixture of benign and neoplastic elements

Marginal Zone Lymphoma

Follicular Colonization

<table>
<thead>
<tr>
<th></th>
<th>Colonization</th>
<th>Normal Follicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCL2</td>
<td>Colonization</td>
<td>Normal Follicle</td>
</tr>
</tbody>
</table>

Follicular Colonization

<table>
<thead>
<tr>
<th></th>
<th>Colonization</th>
<th>Normal Follicle</th>
</tr>
</thead>
<tbody>
<tr>
<td>KI67</td>
<td>Colonization</td>
<td>Normal Follicle</td>
</tr>
</tbody>
</table>
Primary Follicles

- Unreacted follicles
- Germinal center reaction has not occurred
- Composed of mantle zone-type lymphocytes
- Small, mature chromatin, scant cytoplasm
- DDx: May mimic low grade B cell lymphomas

Benign Lymph Nodes

Paraortic Hyperplasia
- Reaction of T-cell zones of lymph node
- Mottled appearance – macrophages and immunoblasts (activated T-cells)
- Will have S100/CD1a positive Langerhans cells present

Causes
- Non-specific/unknown
- Dermatopathic changes – draining region of skin problem
- Viral
- Post-vaccinal

Progressive Transformation of Germinal Centers (PTGC)

- Clinical
  - Most often young, male
  - Single asymptomatic enlarged node
- Partial nodal involvement
- Typically background of follicular hyperplasia
- Large nodule composed of numerous mantle cells with irregular central core of germinal center cells
- No Hodgkin cells
- Eosinophilia common
- Differential Diagnosis: NLPHL, interfollicular CHL

PTGC versus NLPHL

<table>
<thead>
<tr>
<th>Partial nodal involvement</th>
<th>Complete nodal involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of reactive germinal centers</td>
<td>Normal germinal centers not typically present</td>
</tr>
<tr>
<td>Some transformed cells (centroblasts)</td>
<td>LP cells</td>
</tr>
<tr>
<td>Immunochemistry</td>
<td></td>
</tr>
<tr>
<td>T cells scattered</td>
<td>T cell rosettes (CD3, CD5)</td>
</tr>
<tr>
<td>Large cells variable</td>
<td>Large cells strong positive for CD20</td>
</tr>
</tbody>
</table>

pitfalls

Benign Disorders that mimic Lymphoproliferative Disorders
Kimura disease

- Clinical: Young to middle aged male.
- Sites: salivary gland, head/neck
- Histology: Follicular hyperplasia, eosinophilia, polyclonal cells.
- Associated with nephrotic syndrome
- Possible etiologies: virus, ?
- Therapy: resection, steroids, radiation, immunosuppressive therapies
- Prognosis: Good, but recurrence possible

Kimura Disease

Histology

- Follicular hyperplasia
- Eosinophilia
  - Eosinophilic microabscesses
  - Eosinophils within germinal centers
- Polyclonal cells
- Vascular proliferation
  - Increased HEV or activated vascular elements
- Fibrosis

Kimura Disease

Differential diagnosis

- Angiolyphoid hyperplasia with eosinophilia:
  - Note: This is an epithelioid hemangioendothelioma with prominent eosinophilia
  - Also female, superficial site
  - No elevated IGE
  - Older literature confused ALHE with Kimura disease
- Eosinophilia with lymphadenopathy
  - Medications or parasites
- Langerhans cell histiocytosis
- T cell lymphoma
- Hodgkin lymphoma
- Hypereosinophilic syndrome

Acute EBV Infection

Infectious mononucleosis

Clinical
- Patients typically children or young adults
- Young or immunosuppressed
- Flu-like illness, splenomegaly, lymphocytosis, lymphadenopathy

Morphologic
- Distortion of normal architecture
- Follicular hyperplasia
- Paracortical T cell hyperplasia
- AV/Focal necrosis
- Vasculitis
- Capsular inflammation or infiltration
- Large, atypical cells present (may be Hodgkin-like)

Differential Diagnosis:
- Large cell lymphoma, Hodgkin lymphoma

IgG4-related lymphadenopathy
**Associations:**

IgG4-related diseases

- Pachymeningitis
- Hypophysitis
- Lacrimal gland lesion (Mikulicz's disease)
- Sclerosing salivary disease
- Thyroid gland
- Mastitis
- Pulmonary disorders
- Autoimmune pancreatitis
- Hepatitis
- Sclerosing cholangitis
- Retroperitoneal fibrosis
- Prostatitis
- Inflammatory aortic aneurysm
- Tubulointerstitial nephritis
- Lymphadenopathy (80% of cases)
- Skin lesions


**Histology: Lymph Node**

- Diverse findings
  - Reactive follicular hyperplasia
  - Multicentric/PC Castleman-like
  - Interfollicular plasmacytosis and immunoblasts
  - PTGC-like
  - Inflammatory pseudotumor-like
    * fibrosis

*Sato et al., 2010. Cheuk & Chen, 2010.*

**Normal IgG4 staining**

- Lymph Node

**IgG4-related Lymphadenopathy**

- *1 yo male, generalized adenopathy*

**IgG4-related lymphadenopathy**

**Differential Diagnosis**

- Autoimmune lymphadenitis
  - SLE, rheumatoid arthritis
- Multicentric Castleman disease
- PTGC
- "True" inflammatory pseudotumor and other related entities
- Marginal zone lymphoma
- Lymphoplasmacytic lymphoma

**When do I perform IgG4 staining?**

- Follicular or immunoblastic hyperplasias in older adults (50+)
- PTGC in older adults (50+)
- Fibrotic lesions with lymphoplasmacytic infiltrates (inflammatory pseudotumor)
- Anything that looks like Plasma Cell Castleman disease
IgG4-related lymphadenopathy

**SUMMARY**

- Clinical: Older male
- Histology: Lymph nodes showing a broad range of reactive changes
- Possible etiologies: Unknown, possible autoimmune
- Therapy: Steroid and/or rituximab therapy very effective
- Prognosis: Good, but disease may persist despite therapy

Kikuchi-Fujimoto disease

- Clinical
  - Young women
  - More frequent in Asian
  - Some systemic symptoms
  - Benign clinical course
- Preserved architecture
- Necrosis without neutrophils
- Macrophages with crescent shaped nuclei
- Plasmacytoid dendritic cells
- Activated/transformed lymphocytes, immunoblastic appearance
- Differential Diagnosis
  - Large cell lymphoma

Kikuchi-Fujimoto Disease Lymphoma Mimicry

- Large B cell lymphoma
  - Including EBV-associated (with necrosis)
- T cell lymphoma
- "Classic description"

Kikuchi-Fujimoto Disease Histology

- Three phases
  1) Early phase: proliferative
  2) Intermediate phase: necrotizing
  3) Late phase: granulomatous
- Preserved architecture
- Necrosis without neutrophils
- Macrophages with crescent shaped nuclei
- Plasmacytoid dendritic cells
- Activated/transformed lymphocytes, immunoblastic appearance

Kikuchi-Fujimoto disease

- Necrotizing stage

Kikuchi-Fujimoto disease

- CD51/CD123 low magnification
- CD123
Kikuchi-Fujimoto Disease

**SUMMARY**

- Clinical: Young female, isolated cervical nodes
- Histology: necrosis without neutrophils, proliferations of plasmacytoid dendritic cells (CD123 staining)
- Possible etiologies: virus, lupus
- Therapy: Supportive
- Prognosis: Excellent

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**pitfalls**

Precursor/In situ Lesions

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**Follicular lymphoma in situ**

- Clumsy terminology: focal FL, or partial nodal involvement by FL
- Almost always limited stage disease
- Sometimes an incidental finding
- Most cases do NOT progress
- Diagnosed by performance of bcl2 staining on suspicious nodes/follicles

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**FL in situ**

- Up to 70% of "normal" older individuals may have IgH/bcl2 translocations in cells in blood
- Increased incidence with
  - Exposure to pesticides
  - Hepatitis C patients
  - Increased age
- These are not naïve B cells

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**FL in situ**

- 66% - no evidence of follicular lymphoma (28 months average f/u)
- 33% - developed B cell lymphoma
Follicular lymphoma in situ

<table>
<thead>
<tr>
<th>FL</th>
<th>FLIS</th>
<th>FH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bcl2</td>
<td>+</td>
<td>Focally+</td>
</tr>
<tr>
<td>Ki67</td>
<td>Low</td>
<td>Focally low</td>
</tr>
<tr>
<td>CD20</td>
<td>Diffuse positive</td>
<td>Diffuse positive</td>
</tr>
<tr>
<td>Bcl6/CD10</td>
<td>Diffuse positive</td>
<td>Diffuse positive</td>
</tr>
<tr>
<td>CD21</td>
<td>Dendritic cell networks</td>
<td>Dendritic cell networks*</td>
</tr>
</tbody>
</table>

*May be disrupted

FL in situ | Partial involvement by FL
---|-------------------
Normal architecture (low magnification) | At least focally altered architecture
Normal follicles size | Increased size in follicles
Sharp border of follicles | Irregular borders of follicles
Intact mantle zones | Abnormal or attenuated mantles
Scattered | Abnormal follicles are clustered together
Strong bcl2 expression | Weak bcl2 expression
Strong CD10 expression | Weak CD10 expression
Almost pure centrocytes | Mixed cytoologic composition

FL in situ | Partial involvement by FL
---|-------------------
Ki67 low | Ki67 low
By definition "low grade" | Can be higher grade
IgH/BCL2 present | IgH/BCL2 present

*FL in situ can react
Reporting should include number of follicles and percent of node involvement (+% %)

Monoclonal B cell Lymphocytosis

- Monoclonal B cell lymphocytosis
  - CLL-type (e.g. CD5+, CD23+, dim 20, dim st/L)
  - Atypical CLL-type (CD5+, CD23-)
  - Non-CLL type (CD5-, CD10-)
- >40 years old 6.7%
- The abnormal cells persist
- Phenotype remains stable
- FISH
  - Del 13 q 47%, +12 11.8%, ATM deletion 0%
- Almost all CLL are preceded by an MBL phase (90%)

Mantle cell lymphoma in situ

- Minimal involvement of lymphoid tissue by cells with characteristic of mantle cell lymphoma
- Present in mantle zone
- Identified by staining/screening with cyclin D1 stain
- May have non-progressive disease
- BUT... need to stage/clinically evaluate these patients carefully!
Mantle Cell Lymphoma

- SOX-11 (somewhat controversial — not confirmed in larger studies)
  - Conventional MCL +
  - Indolent MCL –

- In normal people those that have IgH/bcl2 in blood have IgH/BCL1 as well!
  - Frequency is about 1/10 of those with t14;18

Mantle cell lymphoma
Clinically indolent!

- Typically leukemic or spleen only disease
- Relatively low peripheral blood counts
- Low grade/small cell morphology (no blastoid or pleomorphic)
- Often CD5 negative
- No evidence of high proliferation
- Often hypermutated Ig (post-GC MCL)
- Simple karyotype
- May lack SOX-11 expression

pitfalls
Misclassification of a Lymphoid Neoplasm
Changes in therapy and/or prognosis

Neoplastic processes with differences in therapy and/or prognosis

- Mantle cell lymphoma versus other small B cell lymphomas
- Follicular lymphoma (FL) grade 2 versus FL grade 3
- DLBCL versus Burkitt lymphoma
- DLBCL prognosis/subtypes
- Hodgkin lymphoma versus DLBCL variants
- Classical Hodgkin lymphoma versus Nodular lymphocyte predominant Hodgkin lymphoma

Mantle Cell Lymphoma

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Small cells, uniform, irregular nuclei, scant cytoplasm; Admixed plump histiocytes</th>
<th>CLL: discyclic FL: dimeric, cleaved MCL: polymorphic</th>
</tr>
</thead>
<tbody>
<tr>
<td>FHC</td>
<td>CD5+ Cyclin D1 +</td>
<td>CLL: CD5 and CD23 FL:CD5, BCL6; NO CD5 MCL: NO CD5</td>
</tr>
<tr>
<td>Genetic</td>
<td>t(11;14)</td>
<td>CLL: various changes FL:t(14;18) MCL: various changes</td>
</tr>
</tbody>
</table>

Mantle Cell Lymphoma

- Specificity of t(11;14) translocation
  - Can be seen in some other tumors
  - Myeloma
- Specificity of cyclin D1 staining
  - Can be seen in other tumors
  - Myeloma, hairy cell leukemia, epithelial tumors
  - USE SOX11 to confirm!
- Variation in clinical behavior
- Range of morphologic appearance
Grading of Follicular Lymphoma

<table>
<thead>
<tr>
<th>Cytology</th>
<th>TCRBCL</th>
<th>CHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background mostly T cells</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Histocytes prominent</td>
<td>Var</td>
<td>Var</td>
</tr>
<tr>
<td>Individual large cells</td>
<td>Y</td>
<td>Y</td>
</tr>
</tbody>
</table>

**IHC**

<table>
<thead>
<tr>
<th>CD15</th>
<th>CD45</th>
<th>CD30</th>
<th>EBV</th>
<th>Oct2/BCB.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Y</td>
<td>Rare (10-30%)</td>
<td>N</td>
<td>YY</td>
</tr>
<tr>
<td>Y</td>
<td>N</td>
<td>Y (-70%)</td>
<td>Y</td>
<td>N/N</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proliferation rate (Ki-67)</th>
<th>TCRBCL</th>
<th>CHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-20%</td>
<td>30-50%</td>
<td>&gt;50%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genetics</th>
<th>TCRBCL</th>
<th>CHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>(14;18)</td>
<td>(14;18)</td>
<td>IGH/BCL6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Therapy</th>
<th>TCRBCL</th>
<th>CHL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade</td>
<td>High grade*</td>
<td>Y</td>
</tr>
</tbody>
</table>

**Burkitt vs DLBCL**

<table>
<thead>
<tr>
<th>(8;14)*</th>
<th>Yes (always)</th>
<th>Some (10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-myc IHC</td>
<td>Yes</td>
<td>Var</td>
</tr>
<tr>
<td>Ki-67&gt;95%</td>
<td>Yes</td>
<td>Occasional</td>
</tr>
<tr>
<td>Homogeneous cytology</td>
<td>Yes</td>
<td>Occasional</td>
</tr>
<tr>
<td>CD10/bcl6</td>
<td>Yes</td>
<td>Some</td>
</tr>
<tr>
<td>BCL-2 by IHC</td>
<td>No</td>
<td>Many</td>
</tr>
</tbody>
</table>

*t Or equivalent translocation

Then, there's the other thing...

- Is there a "adult" version of Burkitt lymphoma?
  - Unequivocally yes
  - Formerly called Burkitt-like
  - Differences are biologic and possibly phenotypic
  - May be "double hit" lymphomas (both t(14;18) and t(8;14))
  - Some may be de novo
  - Have bcl-2 positivity, which is not "allowed" in Burkitt
  - Name "High grade B cell lymphoma, not otherwise specified" has been suggested
DLBCL morphologic subtypes

- IV DLBCL
- T/HRBCL
- Mediastinal type
- CDS+ type
  - Rule out MCL

T/HRBCL vs CHL

- Very large difference in therapy and prognosis
- Most commonly mixed cellularity Hodgkin lymphoma is the subtype
- Significant differences in IHC, and often clinical findings (esp. location) can be helpful

CHL versus TCRBCL

<table>
<thead>
<tr>
<th>IHC</th>
<th>+ (nec)</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD34</td>
<td>(all)</td>
<td>Rare</td>
</tr>
<tr>
<td>PAR5</td>
<td>+ (dim)</td>
<td>+ (strong)</td>
</tr>
<tr>
<td>OCT2/NOB1</td>
<td>+/- (common)</td>
<td>+/- or +/- occasional</td>
</tr>
<tr>
<td>MAMB1</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>EBV/EBER</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>CD20</td>
<td>+/-</td>
<td>+</td>
</tr>
</tbody>
</table>

Hodgkin Lymphoma

- CHL versus NLPHL
- CHL versus TCRBCL
- CHL versus benign processes
  - NLPHL versus PTGC

CHL versus NLPHEL

- Important to recognize
- There is an entity –
  - Lymphocyte-rich classical Hodgkin lymphoma
- This entity is indistinguishable from NLPHEL by morphology alone
- This variant can be easily resolved by IHC
- It is perhaps, less clinically significant, as each are very clinically indolent

LR-CHL versus NLPHEL

<table>
<thead>
<tr>
<th>LR-CHL</th>
<th>NLPHEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lg blue nodules</td>
<td>Y</td>
</tr>
<tr>
<td>Large single atypical cells</td>
<td>Y</td>
</tr>
<tr>
<td>R-S and variants</td>
<td>Y</td>
</tr>
<tr>
<td>Nodules of small B cells</td>
<td>Y</td>
</tr>
<tr>
<td>CD45</td>
<td>N</td>
</tr>
<tr>
<td>CD20</td>
<td>Weak, variable (30%)</td>
</tr>
<tr>
<td>CD15</td>
<td>Y</td>
</tr>
<tr>
<td>CD30</td>
<td>Y</td>
</tr>
<tr>
<td>EBV</td>
<td>Some</td>
</tr>
</tbody>
</table>
pitfalls
Hematopoietic versus Non-Hematopoietic Neoplasm
Mimics and more mimics

Neoplasms that Mimic Mimics of High Grade Lymphomas

- Myeloid sarcoma
- Carcinoma
- Melanoma
- Germ-cell tumors
- Small blue cell tumors
- Thymoma*
- Myeloma/plasmacytoma

*Lymphoma is one of the only mimics that stimulate a both low and grade lymphoma

Lymphoid neoplasm mistaken for non-lymphoid disorders

- ALCL versus non-hematopoietic tumor
- High-grade lymphoma versus small blue cell tumor
- DLBCL versus non-hematopoietic tumor
- ALL/lymphoblastic lymphoma versus non-hematopoietic tumor

Myeloid Sarcoma

Minor clue: Coagulative and eosinophilic necrosis

Metastases

- Not rare, but important as a mimic of:
  - Primary nodal disorders
  - Benign processes
  - Lymphomas
- Types... the usual suspects
  - Breast, lung, GI, neuroendocrine carcinomas
  - Some "small blue cell" sarcomas
  - Rare sarcomas and other neoplasms
**Metastases**

- Clear evidence
- Mimicry of benign lymphoid processes
- Mimicry of neoplastic lymphoid processes

**Carcinoma**

- Undifferentiated Nasopharyngeal carcinoma (UNPC)
- May lose cytokeratin expression
- May be positive for CD30 (10%)
- Express p63
- Likely EBV induced

**Neuroendocrine carcinomas**

- Appear similar to high grade or blastic lymphomas
- Often have more coarse chromatin (salt and pepper)
- May have clustering
- Small amounts of cytoplasm
- IHC:
  - Primary:
    - Positive for keratins (some dot-like positive)
    - Negative for lymphoid markers
  - Secondary:
    - Positive for synaptophysin, chromogranin
    - Immunohistochemistry
    - PITFALLS:
    - Positive for CD56
    - May be positive for PAX5 and tdt

**Scenario**

- Imagine a case....
  - With immunohistochemical expression of:
    - CD56
    - TDT
    - BCL2
    - CD8
  
  **Would this be a lymphoma?**
Metastatic Small Cell Carcinoma

Metastatic NE Carcinoma

Melanoma
- Metastatic melanoma is more often amelanotic
- Cytologic appearance may be fairly uniform large cells and appear monotonous like a large cell lymphoma
- Clinical history and application of IHC stains will distinguish

Germ Cell tumors
- Likely to mimic large cell lymphoma
- Immunohistochemistry
  - Positive
    - Most are keratin positive
  - Pitfalls:
    - CD30 positivity may suggest ALCL diagnosis

High Grade lymphoma versus SBCT
- **HG lymphoid**
  - Lymphoblastic
  - High grade DLBCL
  - Burkitt
  - Some T cell lymphomas
- **SBCT**
  - Neuroblastoma
  - Rhabdomyosarcoma
  - Small cell carcinoma
  - Wilms tumor

Small blue cell tumors
- Wilms tumor, neuroblastoma, rhabdomyosarcoma
- Mimic large cell lymphoma or ALL
- Immunohistochemistry
  - Usual panel of antibodies to include or exclude lymphoma
Thymoma

- Mediastinal location
  - Rarely orchial
- Older (40 years or more)
  - Fairly uniform population of lymphocytes
- Population of slightly larger cells (thymocytes) with open chromatin and poorly defined cytoplasmic borders
- BIC
  - Keratin: defines thymic epithelial cells
  - Secondary
  - TdT: defines immature thymic T cells
Thymoma vs. T-ALL

- Pitfalls:
  - In some cases, epithelial cells will be CD5 positive
  - CD117 may be positive in some cases of both
  - In both lymphocytes will be TdT and CD3 positive
  - Comparable immunophenotype in metastases
    - Thymoma may be seen in pleura or rarely in neck masses

- BOTH
  - Have immature thymic cells present
    - CD5 positive, TdT positive, immature "blastic" appearance
  - Thymoma
    - Shows reticular framework of keratin positive epithelial cells, not present in T-ALL
    - Some cases of epithelial cells will be CD5 positive
    - CD117 may be positive in some cases of both

Lymphoid neoplasm mistaken for non-lymphoid disorders

- ALCL versus non-hematopoietic tumor
- High-grade lymphoma versus small blue cell tumor
- DLBCL versus non-hematopoietic tumor
- ALL/lymphoblastic lymphoma versus non-hematopoietic tumor

Types of Lymphomas that Mimic non-hematolymphoid neoplasms

- Anaplastic large cell lymphoma
- Anaplastic plasmacytoma
- Nodular sclerosis classical Hodgkin lymphoma, syncytial variant
- Diffuse large B cell lymphoma

Hematologic Neoplasms that Mimic Non-Hematopoietic Tumors

- Anaplastic Large Cell Lymphoma (ALCL)
- Syncytial Variant of Classical Hodgkin Lymphoma
- Diffuse large B cell lymphoma
  - Intravascular variant
  - Signet ring form
  - Anaplastic
- Anaplastic Plasmacytoma
- Myeloid sarcoma

Anaplastic Large Cell Lymphoma

- Can mimic non-hematopoietic neoplasms
- Often sinusoidal in distribution
- Appears to be cohesive
- Highly pleomorphic
- Immunohistochemistry
  - CD30 expression
Diffuse Large B cell lymphoma with anaplastic features

- Typical immunophenotype
- However, highly pleomorphic histology suggesting non-hematopoietic neoplasms

Immunohistochemistry
- CD20 expression

Anaplastic Plasmacytoma/Myeloma

- Plasmacytoma/myeloma can have highly anaplastic morphology, especially after therapy
- There are usually some more typical appearing plasma cells

Immunohistochemistry
- CD45 negative
- CD20 negative
- CD3 negative
- Will express kappa or lambda
- CD138 (which can be positive in adenocarcinomas)

Techniques to distinguish lymphomas from mimics

- Careful evaluation of clinical history
  - Never make an "impossible" diagnosis
- Evaluation of other laboratory findings
- Maximize histology
- Immunohistochemical staining
- Immunophenotype (flow cytometry)
- Molecular/genetic testing

ALCL versus Non-HP

- Morphology:
  - Large, anaplastic cells, often in sinuses and forming clusters

IHC mimicry
- EMA+
- Rarely keratin+ (weak and focal)
- CD30+

Thanks for your attention!

A small request...
If you run across interesting or unusual lymph nodes or spleens I would love to see them.
Also, I am in always in need of gross photos of lymph nodes and spleens.

Thanks!!!!!