Morphological and Clinical Features in the Distinction of Benign vs Malignant Lymphoid Proliferations

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Two major types of pitfalls

Over-diagnosis of malignancy
Under-diagnosis of malignancy
(Over-diagnosis of lymphoma is more common, and possibly more harmful, than under-diagnosis)
Examples of common mistakes

• Over-diagnosis of Malignancy
  – Infectious mononucleosis (DLBCL or CHL)
  – Syphilitic lymphadenitis or other reactive conditions (CHL)
  – Kikuchi’s lymphadenitis/Lupus lymphadenitis (PTCL)

• Under-diagnosis of Malignancy
  – Pediatric NMZL/FL (reactive hyperplasia)
  – AITL (reactive hyperplasia)
  – ENKTCL (rhinosinusitis)
  – HSTCL (hepatitis)

• Both
  – PTGC vs NLPHL
Helpful clinical information

• **Age, sex and ethnicity of patient**
  – Children and young adults get different diseases from older people
  – Infections may have atypical presentations in very young or very old (EBV, mycobacteria)

• **Location and extent of lymphadenopathy or other lesions**

• **Systemic symptoms**
  – Fever, sweats, weight loss, pharyngitis
  – Skin rash, myalgias, arthralgias

• **Exposures**
  – Travel to areas of endemic infection
  – Pets, other animals
  – Sexually transmitted diseases (you will NEVER get this history)
Helpful Morphological Features

• Gross
  – Size of lesion
  – Architecture
  – Necrosis

• Microscopical
  – Necrosis (type and location)
  – Architecture
  – Cytology
    » Monomorphous vs polymorphous
    » Cytologically malignant cells present?
Morphology:
The first step = Gross Examination!

Size, consistency
Preservation of hilus
Areas of necrosis
Necrosis
Microscopy: Necrosis

• **Location**
  - Surface (mucosal) – may not be relevant
  - Parenchymal – probably part of the process

• **Type**
  - Apoptosis (single cells – infection, inflammation, some lymphomas)
  - Coagulative (ischemic - infarction, vasculitis, tumor necrosis)
  - Suppurative (neutrophils – pyogenic abscess, CSD, Lues)
  - Caseating (TB, fungus, 3rd syphilis)

• **Association with granulomas**
  - Epithelioid/sarcoidal (sarcoid, TB, fungus, CHL)
  - Suppurative (CSD, brucellosis, tularemia, melioidosis; syphilis)
Microscopy: Architecture preserved?

• Sinuses, cortex, paracortex, capsule intact?
• If not, which compartment is abnormal?
  – Cortex (follicles, monocytoid/marginal zones)
  – Paracortex (immunoblasts, IDC, LC, plasmacytoid DC)
  – Sinuses (histiocytes, Langerhans cells, large lymphoid cells, hemophagocytosis, emperipholisis)
• Extension beyond capsule
  – Does extracapsular component contain atypical cells?
  – Inflammation may be perinodal.
    » Usually polymorphous
    » Loose connective tissue
    » Typically no follicles
    » Look for vasculitis
Are the different cell types where they belong?

- Most lymphoid neoplasms are composed of cells normally found in lymphoid tissues
  - SL, CB, CC, IB, PC, MZ, MBC
- Finding them in the wrong place or in abnormal numbers suggests lymphoma
  - Centrocytes outside of follicles – FL?
  - Prominent extrafollicular collections of MZC or MBC – MZL?
  - Immunoblasts/plasmablasts in confluent sheets or sinuses – DLBCL?
  - Langerhans cells in sinuses w/eos – LCH?
Morphological Features

- **Monomorphous vs polymorphous cellular composition**
  - Polymorphous
    - Benign/reactive
    - Hodgkin lymphomas
    - PTCL such as AITL

- **Are cytologically malignant cells present?**
  - Not all “atypical cells” are abnormal (immunoblasts, binucleate plasma cells)
  - Rare lymphomas contain cells not found in normal tissues
    - HL – RS cells (lacunar, classical, LP)
    - ALCL, other PTCL with hyperchromatic, bizarre or unusual cells
    - Some DLBCL with anaplastic or bizarre morphology
12 year-old boy

- Fever, sore throat, enlarged cervical lymph nodes, splenomegaly
- Tonsils enlarged, airway obstruction, peritonsillar abscess
- Tonsillectomy performed
Necrosis
Tonsil Immunoblasts, mitoses
Diagnosis: Infectious Mononucleosis

- Patient had a positive heterophile test and was known to have IM, complicated by peritonsillar abscess.
- Despite this, the pathologist made a diagnosis of diffuse large B-cell lymphoma.
- Diagnosis was “confirmed” at a university hospital where the patient went for treatment.
- A third consultant made the diagnosis of lymphoid proliferation due to acute EBV infection.
- The child recovered spontaneously.
Infectious Mononucleosis: Clues

- Paracortical expansion, distortion of architecture
  - Reactive follicles typically present
  - Lymph node sinuses patent

- Zonal necrosis, usually surface (tonsil)

- Polymorphous lymphoid population:
  - Small and medium-sized lymphoid cells, immunoblasts, plasma cells
  - Single cell necrosis (apoptosis)
  - Frequent mitoses and focal sheets of immunoblasts
  - Binucleate immunoblasts (may resemble Reed-Sternberg cells)

- Blasts:
  - CD20+ Bcl6- Mum1+ CD30+/− CD15- EBER+ K>L

- Other lymphoid cells:
  - CD3+T cells, CD4<CD8
21-year-old female college student

- Noted a nontender inguinal mass
- Reportedly had upper respiratory symptoms 2-3 weeks earlier, treated with antibiotics
- 2 cm and 1.2 cm nodes were excised
Diagnosis

- Acute Epstein-Barr virus infection (infectious mononucleosis), probably recovering
- Positive IgM and IgG anti EBV VCA antibodies, negative EBNA
- Confirms recent EBV infection
- PCR for *IGH* and *TCR* clonality
  - *IGH* polyclonal
  - *TCR* – positive for a clonal *TCR* gamma gene rearrangement
    » Dominant clone in an oligoclonal background
    » Clonal T-cell responses to EBV occur and may persist in blood for years (memory CD8+ cells)
Infectious Mononucleosis

• Adolescents, young adults
  – May affect young children and older adults (often clinically atypical)

• Atypical features
  – Absence of pharyngitis, non-cervical lymphadenopathy, splenomegaly only
  – Heterophile–negative (young children, wrong timing), absence of EBV-specific antibodies (early)

• Complications:
  – Splenic rupture, hemophagocytic syndrome, Guillain-Barre syndrome
  – *Biopsy or tonsillectomy resulting in a diagnosis of lymphoma*
Infectious Mononucleosis: How to stay out of trouble

• Be aware of the clinical history before making a final diagnosis
  – Be very careful of making a diagnosis of EBV+ lymphoma in a patient known to have IM!

• Be aware of the anatomy
  – Tonsil is an unusual site for lymphoma in young people

• And the architecture
  – Preserved follicles, necrosis restricted to the surface

• And the cytology
  – Polymorphous, maturation, single cell necrosis
39-year-old man

- Enlarged right inguinal lymph node; no other history
- 2.8 cm in diameter LN excised
- Flow cytometry
  - Predominance of B cells, polytypic
  - T cells with normal antigen expression
- Immunohistochemistry at referring hospital
  - Large CD30+ cells, suspicious for Hodgkin's lymphoma.
Plasma cells
Special stains

- Immunoblasts in the paracortex: CD30+ CD15-
- Acid fast, Fite, fungal stains, Warthin-Starry, Brown-Hopps, Giemsa negative for organisms.
Diagnosis

Syphilitic lymphadenitis
Lymphadenitis due to *t. pallidum*

- Fibrosis, plasma cells, and large poorly-formed granulomas with neutrophilic necrosis are characteristic of secondary syphilis.
  - Architectural distortion may be marked.
- Acute necrotizing lymphadenitis may be seen in early infection.
- Caseating necrosis (gumma) may be seen in late infection (rare these days).
- Perinodal fibrosis and inflammation with plasma cells.
  - Frequent obliterative endarteritis (perinodal).
Lymphadenitis vs CHL

- Other examples: toxoplasmosis, CMV, EBV
- In CHL, the most atypical cells are found in areas with epithelioid cell clusters, granulomas, necrosis.
- In reactive lesions, immunoblasts are in paracortex, often distinct from granulomatous areas.
- Avoid doing CD30 and CD15 stains if you do not see cytologically malignant cells!
  - Immunoblasts will always be CD30+.
  - Histiocytes may be CD15+ and misinterpreted as RS cells.
  - You will find positive cells, and then what will you do?
41-year-old woman

- Cervical lymphadenopathy
- Brief history of low-grade fever, malaise
- Excisional biopsy
Kikuchi's necrosis
Diagnosis

• **Immunophenotype**
  – Flow - normal T and B cells
  – Immunoblasts: CD3+ CD8+ T cells
  – Plasmacytoid dendritic cells: CD68+ CD123+

• **Kikuchi’s disease**
  – Rule out systemic lupus erythematosus

• **Pitfall: Peripheral T-cell lymphoma**
Lupus Lymphadenitis:
Hematoxylin bodies
Kikuchi’s/SLE: Clues

• **Clinical features**
  – Young woman > man
  – Cervical (or axillary) lymphadenopathy
  – Systemic symptoms, history or serology of SLE

• **Morphology**
  – Paracortical expansion with small germinal centers, sinuses preserved
  – Aggregates of plasmacytoid dendritic cells
  – Heterogeneous composition of necrotic areas
    » Apoptotic necrosis, cellular debris
    » Crescentic histiocytes
    » Hematoxylin bodies (if you’re lucky)

• **Immunophenotype – in context of other features**
  – Plasmacytoid dendritic cells: CD68+ CD123+
  – Immunoblasts: predominantly T cells
    » Most large-cell lymphomas are B cell

• **Think twice before making a diagnosis of PTCL in a young woman!**
46 year-old Hispanic-American man*

- Nasal congestion, chronic sinusitis
- Opacification of frontal and ethmoid sinuses
- Biopsies of nose, sinus
- Dense lymphoid infiltrate
- Consultation because of suspicion of MALT lymphoma

*in the US this term refers to descendants of native Americans [of presumed East Asian origin] who intermarried with Spanish settlers.
Diagnosis

Extranodal NK T-cell lymphoma, Nasal type
Comment

• Extranodal NK/T-Cell Lymphoma Nasal Type with a Predominance of Small Cells: Challenging Diagnosis of a Putative Early Lesion (Sohani et al, EAHP 2010)
  – Six cases, most misdiagnosed on first biopsy as benign
  – 5/6 expected ethnicity (Hispanic/Native American)
  – Initial indolent course, but 4/6 recurred and 3/5 died of disease at 4, 10, and 14 months

• Clues to the diagnosis
  – Dense lymphoid infiltrate
  – Involvement of bone (not seen in rhinosinusitis)
  – Mild cytologic atypia
  – Do more than one T-cell stain!
Benign vs Malignant: How to stay out of trouble

• Know the clinical features: do they suggest a reactive or infectious process?
• Check the gross: is the architecture preserved?
• Look at cytologic features in the context of architecture:
  – Is the process involving appropriate compartments of the lymph node?
  – Are all the cells where they belong?
Benign vs Malignant:
How to stay out of trouble

• Are there cytologically malignant cells?
  – “Cytologically malignant” cells are those that don’t belong anywhere in a lymph node

• Special studies – interpret in context of morphology, clinical features
  – Clonality studies (IHC, ISH, PCR) – beware false + and –
  – Abnormal antigen expression
  – Stains for micro-organisms, viruses (spirochetes, Bartonella, EBV, CMV)

• Don’t order a study without knowing what you will do with the information!
  – If you don’t see malignant cells, don’t order CD15 and CD30…
Benign vs Malignant:
How to stay out of trouble

• Communicate with clinicians.
  - Clinical information may help establish diagnosis.
  - Don’t be insulted if they question your diagnosis - they can save you from mistakes.
  - An informed clinician is the pathologist’s best friend!

• Don’t be afraid to say you aren’t sure what it is.
  - Indicate the differential diagnosis.
  - Indicate the reason for the problem (inadequate material, unusual case, more info needed).
  - Indicate how it can be solved (another biopsy, genetic studies, clinical information).

• Don’t be afraid to ask for consultation.
  - Intra- or extra-departmental…
  - This is not a sign of weakness!