HEMATOPATHOLOGY FOR CYTOPATHOLOGISTS

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McKee Cytology Symposium

I HAVE NOTHING TO DISCLOSE
What I won’t be discussing.

- CSFs – nobody can save these
- Exhaustive review of CD markers
- 7,000+ Lymphoma Classifications by the WHO
- 7,000+ Benign Lymphadenopathy Classifications
- Bone marrow aspirates
- Coagulation Cascade
- Histopathology of esoteric lymphomas
- DSMIV Classifications of Hematopathologists' Personalities
- T-Cells

REASONABLE,
NOT OBSESSIVE

Overview – Case based discussion

• Do you hear what they’re saying about us? – It may surprise you.
  - Case 1

• Monomorphic Populations of Lymphocytes - The Precious, The Few, The Monotonous Lymphomas
  - Case 2
  - Case 3

• Benign Lymphadenopathy Simplified – Reasonable, not obsessive, remember?

• Do you hear what they’re saying about us? – It may surprise you.
  - Case 4
  - Flow Cytometry – Primer or Review; Choose Your Own Adventure
  - Case 5
  - Case 6

• Other Hematolymphoid Neoplasms – The Unusual Suspects
  - Case 7

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DO YOU HEAR WHAT THEY'RE SAYING ABOUT US? 
It may surprise you.
Do you hear what they’re saying about us?

- 20% of primary or recurrent lymphoma will undergo FNA
- Obvious benefits of the FNA
- Prevailing view is that a primary diagnosis should be confirmed by biopsy
- FNA may be 1st line diagnostic procedure for the pathologic diagnosis of lymphadenopathy
- It is accepted in HEMEPATH literature and textbooks that FNA for the diagnosis lymphadenopathy in adult and pediatric patients is 94% Sensitive and 99% Specific

What is the accepted sensitivity and specificity of fine needle aspiration (FNA) for the diagnosis lymphadenopathy in adult and pediatric patients?

A. 53% sensitivity; 54% specificity
B. 27% sensitivity; 72% specificity
C. 78% sensitivity; 79% specificity
D. 94% sensitivity; 99% specificity

Do you hear what they’re saying about us?

- We can do this
- In fact, we do a great job of suspecting and diagnosing lymphomas
- Stay with me – I’ll show you
Case 1

60 year old

- Neck mass
- History of Sjogren’s Syndrome
Case 1
60 year old
• Neck mass
• History of Sjogren’s Syndrome

CD3 CD20
CD5 BCL1

CD19 – PE
CD5 – FITC
What is the diagnosis?
A. Benign Reactive Lymph Node
B. Atypical Lymphocytes
C. Small Lymphocytic Lymphoma
D. Follicular Lymphoma
E. Mantle Cell Lymphoma

Case 1
60 year old

• Cytologic Diagnosis
  • Small B-Cell Lymphoma
  • Monomorphic population of lymphocytes are present with round regular nuclei with coarsely clumped chromatin. Flow cytometric analysis reveals a clonal B-cell population.

• Surgical Diagnosis
  • Chronic Lymphocytic Leukemia / Small Lymphocytic Lymphoma

• Clinical Follow-up
  • "This is unlikely to be a CLL/SLL in a patient with Sjogren’s. Additionally, it is stage I. Are you sure that it is not a Marginal Zone Lymphoma?"
Monomorphic Populations of Lymphocytes

- Surrogate terminology to mean it “looks” monotypic or clonal
  - Small-Cell Lymphomas or Low-Grade Lymphomas
  - Small Cell Lymphomas
  - Lymphoplasmacytic Lymphomas
  - Small Cleaved-Cell Lymphomas

- Because Polymorphic Population of Lymphocytes means it “looks” polytypic or reactive

Monomorphic Populations of Lymphocytes

- Small Mature B-Cell Lymphomas
  - Small Cell Lymphomas → CLL/SLL, perhaps Mantle Cell Lymphomas
  - Lymphoplasmacytic Lymphomas → Marginal Zone Lymphoma
  - Small Cleaved-Cell Lymphomas → Follicular Lymphoma
Monomorphic Populations of Lymphocytes

- CLL/SLL
  - Composed of two cell populations
  - Small round lymphocytes with coarsely clumped chromatin
  - Prolymphocytes, fewer in number, larger, prominent “cookie cutter” nucleoli

- Mantle Cell Lymphoma
  - Legitimately monotonous population - not large - intermediate sized
  - Delicate clefts; not specifically cleaved, dispersed chromatin
  - Blastoid variant - large cells with nucleoli

- Marginal Zone Lymphoma and Lymphoplasmacytic Lymphoma
  - Composed of small lymphocytes, plasmacytoid lymphocytes, plasma cells, and immunoblasts

- Follicular Lymphoma
  - Composed of centrocytes (small cleaved lymphocytes) and centroblasts in varying proportions
  - Admixed are Follicular Dendritic Cells and tangible body macrophages

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CASE 2

63 year old

- Lymphadenopathy
- Abdominal pain

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Case 2
63 year old
- Lymphadenopathy
- Abdominal pain
What is the diagnosis?
A. Benign Reactive Lymph Node
B. Atypical Lymphocytes
C. Small Lymphocytic Lymphoma
D. Follicular Lymphoma
E. Mantle Cell Lymphoma

Case 2
63 year old
• Cytologic Diagnosis
  • B-Cell Lymphoma
  • Polymorphc population of lymphocytes showing tangles of smeared nuclei. The nuclei are enlarged and frequently cleaved. Flow cytometric analysis reveals a clonal B-cell population.
• Surgical Diagnosis
  • Follicular Lymphoma (Grade 1-2)

Case 2.5
85 year old
• Follicular Lymphoma
• Small cleaved-cell lymphoma – this is a beautiful descriptor

• Long-standing history of Follicular Lymphoma
• New onset ascites
CASE 3

72 year old

- History of Lymphoplasmacytic Lymphoma
- Diagnosis made on bone marrow biopsy – not available for review
- New 16cm retroperitoneal mass
- Ascites fluid – because that’s a reasonable specimen
Case 3
72 year old

• History of Lymphoplasmacytic Lymphoma
• Diagnosis made on bone marrow biopsy – not available for review
• New 18cm retroperitoneal mass
• Ascites fluid – because that’s a reasonable specimen
What is the diagnosis?

A. Positive for Lymphoma – consistent with patient's diagnosis
B. Positive for Malignant Cells
C. Atypical Lymphocytes
D. Reactive Mesothelial Cells
E. Melanoma

Positively for Malignant Cells
Atypical Lymphocytes
Reactive Mesothelial Cells
Melanoma

Case 3
72 year old

Cytologic Diagnosis
- Positive for Malignant Cells, Consistent with Plasma Cell Neoplasm
- Malignant plasmacytoid cells are present. These cells have voluminous cytoplasm and markedly irregular nuclei and nucleoli. Mitotic figures are readily identified.

Surgical Diagnosis – still waiting for that biopsy
- Now her diagnosis is listed as “Rare Aggressive Lymphoplasmacytic Malignancy”

Monomorphic Populations of Lymphocytes

- Very few lymphomas are actually monomorphic
- ALL CD5+ lymphomas should be interrogated for Mantle Cell characteristics – ALL OF THEM
- Cytologic atypia within a polymorphic population remains cytologic atypia
- Don’t be unreasonable just because there’s a weird heme diagnosis
Benign Lymphadenopathy Simplified

- Lymphadenitis – infectious or inflammatory
  - Acute
  - Granulomatous
- Reactive Lymphoid Hyperplasia – diverse and diagnostically challenging
  - Involvement Patterns
    - Paracortical Hyperplasia
    - Follicular Hyperplasia
    - Sinus Expansion

Commonly Sited Features that Favor Reactive Lymphoid Hyperplasia
- Polymorphic population
- T-Cells > B-Cells
- Tingible Body Macrophages
- Frequent Mitoses

The Features that I think Favor Reactive Lymphoid Hyperplasia
- No large atypical cell population
- Lymphocytes with HIGH N/C
- The radiologist doesn’t know why it needs a biopsy
- Lymph node size < 2 cm
Which of the following is **false** regarding differentiating between neoplastic and non-neoplastic lymphoid hyperplasias?

A. The smear pattern and lymphocyte population vary considerably based on the stage of the reactive process and compartment of the lymph node that the process primarily affects.

B. A high mitotic rate can be seen in both neoplastic and non-neoplastic lymphoid hyperplasias.

C. A polymorphic population is the best indicator of a non-neoplastic process.

D. B and T-cell lymphomas and Hodgkin lymphomas are the most often encountered in clinical practice.
Case 4
50 year old
- Para-aortic lymphadenopathy
- History of Renal Cell Carcinoma
What is the most appropriate response to you surgical pathologist friend?
A. Let it go – looks reactive
B. There were some really bad cells cytologically. Let’s order some more stains.
Case 4
50 year old
- Para-aortic lymphadenopathy
- History of Renal Cell Carcinoma

Cytologic Diagnosis
- Suspicious for malignant cells
- Polymorphic population of lymphocytes showing very rare, markedly atypical cells.

Surgical Diagnosis
- CD30+ Anaplastic Large Cell Lymphoma

Benign Lymphadenopathy
- If the lymph node is less than 2cm, let it go
- Small mature B-cell lymphomas can be missed and it's okay:
  - P.S. Flow should catch those
  - Large atypical cells should not be let go
  - CX force here to take the fall
Each tube has only 4 different fluorochromes conjugated to 4 different antibodies.
Flow Cytometry – Lasers

- CD5
- CD19
- CD10
- CD45

Flow Cytometry – Data Output

- All the data for each cell collected as “events”
  - Three pieces of information for each event
    - Size
    - Complexity
    - Fluorescence
- User defined axes for each graph
- Isn’t that nice?

Flow Cytometry – Examples

- Clonal B-cells – Kappa Restricted
- Kappa vs. Lambda
Flow cytometers give information about a cell’s internal complexity and size. Which of the following is the correct pairing?

A. Forward scatter is an indicator of size, and side scatter is an indicator of internal complexity.
B. Forward scatter is an indicator of internal complexity, and side scatter is an indicator of size.
C. The ratio of forward scatter to side scatter is an indicator of size, and side scatter is an indicator of internal complexity.
D. Forward scatter and side scatter are used to determine a cell’s viability, not to indicate size or internal complexity.

Flow cytometry is no longer ancillary – just like immunostains or molecular – it’s expected. We need to understand and use it. Not that complicated. The pre-analytical phase is still the most important. If you don’t enjoy getting blank requisitions, don’t send the flow cytometry lab blank requisitions.
When Flow Fails

- My Experience
  - To flow is better than not to flow – even when large cells are the question
  - 16% failure to detect a donor population by flow despite diagnostic material of both large and small cell lymphomas
  - Size is often cited as a cause

- Large is bigger than an endothelial cell nucleus (17-20μm)
- Most flow cell apertures are 150μm or greater

Case 5
Case 4
60 year old
- Previous lung nodule – Suspicious for Focal Diffuse Large B-cell Lymphoma
- FNA of that very same lung nodule
Case 4
60 year old
• Previous lung nodule – Suspicious for Focal Diffuse Large B-cell Lymphoma
• FNA of that very same lung nodule

What is the diagnosis?
A. Atypical Lymphocytes
B. Suspicious for Malignant Cells
C. Positive for Malignant Cells
D. Large B-cell Lymphoma
Case 4
60 year old
• Cytologic Diagnosis
  • Large B-Cell Lymphoma
  • Polymorphic population of lymphocytes showing scattered large malignant lymphocytes. Immunohistochemical staining of smears reveals these cells to be B-cell lineage. Flow cytometric analysis shows no B-cells, likely due to sampling or poor viability.

• Surgical Diagnosis – performed 11 months later, para-spiral mass
  • Diffuse Large B-cell Lymphoma, Activated B-cell Subtype

Case 5
22 year old
• Presents with shortness of breath
• Large anterior mediastinal mass

Slide: Case 6

CASE 6

Slide: Case 6

Slide: Case 6

Slide: Case 6
Case 5
22 year old
- Presents with shortness of breath
- Large anterior mediastinal mass

What is the diagnosis?
A. Positive for malignant cells
B. Atypical Lymphocytes
C. Hodgkin Lymphoma
D. Thymoma

Cytologic Diagnosis
- Positive for Malignant Cells
- Polymorphic population of lymphocytes showing scattered large malignant lymphocytes in a background of small lymphocytes, plasma cells, and scattered eosinophils. The malignant lymphocytes show bizarre and anaplastic forms. There are frequently binucleate forms, consistent with Reed-Sternberg cells.

Surgical Diagnosis
- Nodular Sclerosis Classical Hodgkin Lymphoma
When Flow Fails

• If it’s malignant, it’s still malignant
  • Even as a primary diagnosis
  • Just “Malignant” is fine if it is not unequivocally lymphoma
• I support running B and T cell tubes on all cases
  • There are characteristic findings in T-cells

Other Hematolymphoid Neoplasms

• Trilineage hematopoiesis
  • Leukocytes
  • Erythrocytes
  • Thrombocytes
• Leukemias
  • Lymphocytic
  • Myeloid
Other Hematolymphoid Neoplasms

- Why cytopathologists should care:
  - CSFs
  - FNAs of masses

- Just like squamous vs. adenocarcinoma – the difference matters
- If we can't tell, I recommend the use of the term "hematolymphoid"

CASE 7

- 50 year old
- History of Acute Myeloid Leukemia
- Bilateral Preauricular masses
Case 6
50 year old
• History of Acute Myeloid Leukemia
• Bilateral Preauricular masses

What is the appropriate diagnosis?
A. Positive for lymphoma; B-cell screen flow cytometry.
B. Atypical lymphocytes; B-cell screen flow cytometry.
C. Positive for malignant cells; Acute leukemia flow cytometry.
D. Lymphocytes present; Attempt cell block for immunostains.

Cytologic Diagnosis
• Positive for Malignant Cells
• Malignant cells showing marked nuclear pleomorphism, fine chromatin, nucleoli, and granulated cytoplasm are present. The findings are consistent with the patient’s known Acute Myeloid Leukemia. In the appropriate clinical setting of a destructive mass lesion, the diagnosis is Myeloid Sarcoma.

Surgical Diagnosis – the patient died a week later
• Autopsy showed myeloid blast infiltrates and masses, everywhere
Reasonable Conclusions

• Focus on the cytologic features
• Smear description should match the actual smear
• Don't force square pegs in round holes
• Understand flow cytometry and USE it
• Lymphoid and myeloid lineages are different
• We’re good at this; we are still expected to be.

References


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