Lymph node cytopathology: A practical approach to lymphoproliferative disorders

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Diagnostic use of FNA in lymph node pathologies

• **Well-established:**
  - metastatic malignancy,
  - lymphoma recurrences
  - some reactive or inflammatory disorders: Tuberculosis, sarcoidosis

• **Diagnostic sensitivity/accuracy:** usually above 95%

• **Controversial:**
  - primary lymphoma diagnosis
  - Diagnostic sensitivity varies from 12% to 96%

Academic institutions: high level diagnostic accuracy
Community practice: the accuracy rate significantly low
Multiparameter approach is critical for definitive lymphoma diagnosis

- Cytomorphologic features alone are not sufficient for the diagnosis of primary lymphoma
- Immunophenotyping with flow cytometry and/or immunocytochemistry is mandatory
- In selected cases molecular/cytogenetic analyses are required for definitive lymphoma classification
Lymph node pathologies

- 1-Reactive lymphoid hyperplasia/inflammatory disorders
- 2-Lymphoid malignancies
- 3-Metastatic tumors
Common problems in lymph node cytology

• Reactive lymphoid hyperplasia vs lymphoma
• Primary lymphoma diagnosis (lymphoma subtyping)
• Predicting primary site of metastatic tumor
• Nonlymphoid tumors mimicking lymphoid malignancies
• Correct diagnosis of specific benign lymphoid lesions
Problem 1: Reactive vs lymphoma
Case 19- years-old boy
Multiple bilateral cervical LAPs for 4 weeks
FNA from the largest cervical lymph node measuring 15X13 mm
No further clinical story
Follicular center cells

Polymorphic lymphoid cells

- Follicular center cells
- Polymorphic lymphoid cells
- Centroblast
- Centrocyte
- Reactive T lymphocyte
- Dendritic cell
- Centrocyte
Dendritic cells
Lymphohistiocytic aggregates and tingible body macrofages
Reactive Follicular Hyperplasia diagnosis

- Clinical story: Shortest diameter of lymph node usually not more than 15mm
- Children, young adults
- Polymorphous lymphoid cells
- Lymphohistiocytic aggregates
- Immunophenotyping:
  - Mixed lymphoid population
- No monoclonality in flow cytometry
- PCR: No B-cell or T-cell arrangement
Differential diagnosis
Low grade lymphoproliferative disorders

- Morphological distinction can be extremely difficult
- Clinical story
- Use of flow cytometry and immunohisto/cytochemistry are necessary in some instance
Problem 2: Reactive paracortical hyperplasia vs lymphoma
Viral(EBV) lenfadenitis
A case of varicelle zoster lymphadenitis in a 29 y-o primary school teacher
Reactive paracortical hyperplasia

Viral lymphadenitis:
EBV, HSV, CMV
Postvaccinial lymphadenitis
Dilantin hypersensitivity

For correct diagnosis

- Clinical history

Blood analysis for viral antibodies

- IHC

- FCI: no B cell clonality

- PCR: no T-cell clonality
Problem 3: Identifying specific reactive lymphoid disorders

Granulomatous lymphadenitis
(Tbc, sarcoidosis, tularemi, CSD)
Toxoplasma lymphadenitis
Castleman disease
Kikuchi lymphadenitis
SLE lymphadenitis
Rosai-Dorfman Disease
Dermathopathic lymphadenopathy
Toxoplasma lymphadenitis

- Posterior cervical triangle lymph node involvement
- Clinical story
Lab features (Anti-Toxo IgM positivity)
Microgranulomas
Follicular hyperplasia
Identification of microorganism in macrofages
Case 2: 42 y-o female patient, persistent solitary cervical LAP measuring 23X12 mm
Kikuchi Lenfadenitis (necrotising histiocytic lymphadenitis)
58 y-o male patient with parotid mass
Problem 4: Correct subtyping of low-grade chronic B-lymphoproliferative disorders

- CLL/SLL
- LPL
- Mantle cell lymphoma
- Follicular lymphoma
- Marginal zone lymphoma
Case 3: 58-year-old male, multiple cervical lymphadenopathy
WBC: 16000, PBA: 60% of lymphocytes
Clumped chromatin
paraimmunoblast  prolymphocyte
CD19+/CD5+/CD23+
Lambda-monoclonal
CLL/SLL

- Absolute lymphocytosis (more than 5000/ml)
- Patients are mostly middle aged or elderly
- Monotonous lymphoid infiltration
- Small lymphocytes with clumped chromatin
- Prolymphocyte, paraimmunoblast
- Flow cytometry: CD5+, CD23 +, FMC-7 -
- B cell monoclonality
- Ki-67 index low: usually less than 30%
Case 4: 56 y-o male with multiple LAPs including cervical, axillary and inguinal regions
Right axillary LAP, 3 cm in the largest diameter
centroblast

FDRC

centrocyte
Low grade follicular lymphoma (grade 1,2)
CD20
CD10
Bcl-2
Bcl-6
Ki-67
Follicular lymphoma (grade 1,2)

- 30-40% of all lymphomas
- Occur at any age
- Cellular smear, sometimes showing nodularity
- Polymorphic lymphocytes including centrocytes, centroblasts

- IHC: bcl2+, bcl6 +, CD21+, CD23 +, CD10 +
- Ki-67 index: Less than 30%
- FCI: B cell monoclonality
- FISH: t(14,18)
Case 5: 55-years-old lady with multiple cervical, axillary, abdominal, and inguinal LAPs
FNA from right axillary lymph node with 25 mm in diameter
Medium sized atypical lymphoid cells with less nucleus contour irregularity
CD5(+) / CD23 (-)
Monoclonal
Mantle cell lymphoma

CD20

CD3

BCL-1

Ki-67
Mantle cell lymphoma

- 7-8% of all lymphomas
- Usually occur in older adults
- Aggressive course
- Monotonous infiltration
- Centrocyte like cells without centroblasts
- Slightly irregular nuclear contours
- Small distinct nucleoli
- Plasma cells or plasmacytoid cells may be observed

Immunophenotype:
- CD5+, CD23 –, CD10 –, Bcl-2 +,
- bcl-1/cyclin D1 +, SOX-11 +
- FISH: t(11,14)

Variants
- blastoid
- pleomorphic
Case 6: 62 y-o lady, FNA from right parotid masss with 24 mm in diameter,
Polymorphic lymphoid infiltration

- Monocytoid cells
- Centrocytic cell
- Plasmacytoid cell
Marginal zone lymphoma: Lymphoepithelial lesion

Heterogenous population
Centrocytic cells
Monocytoid B cells
Plazma/plasmacytoid cells
Lymphoepithelial lesion

CD5 –
CD23–
CD21+
CD10–
BCL-1 –
BCL-2 +
BCL-6 –
Ki-67 index: low

Flow cytometry: Monoclonal B cell population
<table>
<thead>
<tr>
<th>Sample Type</th>
<th>Clonal Type</th>
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<tbody>
<tr>
<td>Negative control</td>
<td>polyclonal</td>
</tr>
<tr>
<td>Positive control</td>
<td>monoclonal</td>
</tr>
<tr>
<td>Case</td>
<td>monoclonal</td>
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</tbody>
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Detection of PCR products by capillary electrophoresis (fluorescent primers)

Polyclonal Pattern

Clonal Pattern

“Lineage infidelity”

<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>Clonal IgH rearrangement</th>
<th>Clonal TCR rearrangement</th>
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</thead>
<tbody>
<tr>
<td>Mature B-NHL</td>
<td>&gt;99%</td>
<td>5-7%</td>
</tr>
<tr>
<td>Mature T-NHL</td>
<td>4-6%</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>B-ALL</td>
<td>&gt;99%</td>
<td>20-40%</td>
</tr>
<tr>
<td>T-ALL</td>
<td>10-15%</td>
<td>85-95%</td>
</tr>
</tbody>
</table>
Problem 5: Correct subtyping of large cell lymphomas
Case 7: 83 y-o female patient with huge adrenal mass and conglomerated intraabdominal LAP, 6 cm in diameter. FNA from intraabdominal mass under CT-guidance.
Large atypical lymphoid cells with prominent nucleoli (dominantly immunoblastic)
DLBCL- centroblastic
DLBCL, centroblasts and ring shaped anaplastic cells
DLBCL

- 35-40 % of lymphomas
- Large cells:
  - **Centroblastic**: noncleaved cell with multiple marginal nucleoli
  - *Immunoblastic*
  - **Pleomorphic (anaplastic)**: cells resemble RS cells or cells of ALCL
- Immunophenotype: CD20 +,
- bcl-2, bcl-6 CD10, and MUM-1 variable +,
- Ki-67 index: usually more than 50%
Other variants/subtypes

- TCRBCL
- Primary mediastinal (thymic) large B-cell lymphoma
- CD5+ de novo DLBCL
- EBV + DLBCL of elderly
- Lymphomatoid granulomatosis
- ALK+ large B-cell lymphoma
- Primary DLBCL of CNS
- DLBCL associated with chronic inflammation
- Plasmablastic lymphoma
- PEL
Differential diagnosis

- Other large cell lymphomas (PTCL, ALCL, Plasmablastic lymphoma, PEL, PTLD)
- Burkitt lymphoma
- Hodgkin lymphoma
- Viral lymphadenitis
- Plasma cell malignancies
- AML
- Nasopharynx carcinoma
- Poorly differentiated carcinomas
- Thymoma
- Germ cell tumors
- Melanoma
- Small blue round cell tumors: ES/PNET, RMS, NB
Case 8: 25 y-o male, Right iliac wing (pelvic bone) mass 7 X 5.5 cm in diameter
Abscess ?, osteomyelitis ?, ES/PNET ?
HALLMARK CELLS
PTCL -NOS
Problem 6: Hematolymphoid tumors with blastic morphology

- Precursor T and B lymphoblastic lymphoma
- Burkitt lymphoma
- Burkitt-like (grey zone) lymphoma
- MCL-blastoid variant
- AML(M0-M1)
- Blastic plasmacytoid dendritic cell tumor

Relatively uniform cell population
Medium sized smooth or convoluted nuclei with inconspicuous nucleoli
Delicate powdery (blastic) chromatin
Scanty fragile pale blue cytoplasm
Starry-sky pattern
High mitotic index
Precursor B- lymphoblastic lymphoma
Immunophenotype
CD20+
CD10 +
Tdt +
Ki-67 index: high > 50%
Case 10: 4 y-o girl with large intraabdominal mass and had peritoneal effusion
Starry -sky pattern
Burkitt lymphoma
C-MYC (8q24) Break, TC KBI-10611
Problem 7: Hodgkin lymphoma diagnosis (RS vs RS-like cells)

- TCRBCL
- ALCL
- Viral lymphadenitis
- DLBCL
- T cell lymphomas
- Gray-zone lymphomas
- Nasopharynx carcinoma
Case 10: 24 y-o male patient. Left cervical LAP, 25 mm in size
Classical Hodgkin lymphoma
Most 15-35 years
Cervical, mediastium and axillary lymph node involvement most frequent
B symptoms +
RS cells and mononucleated Hodgkin cells
Reactive background: lymphocyte, eosinophil, histiocyte, plasma cells
CD15, CD30

PAX-5

LMP-1

MUM-1
Nodular lymphocyte predominant Hodgkin lymphoma
LH cells (popcorn cells)
Problem 9: Plasmacytoid lesions

- Reactive plasmacytosis
- Castleman disease
- Nodal plasmacytoma
- Marginal zone lymphoma
- Mantle cell lymphoma
- Lymphoplasmocytoid lymphoma
- DLBCL immunoblastic
- Plasmablastic lymphoma
- Primary effusion lymphoma
- Immune deficiency associated lymphoproliferative disorders
Nodal Plasmacytoma
Anaplastic myeloma
Case 11: 5- y-o boy with renal transplant recipient
18 months after transplantation, FNA from Intraabdominal/paraortic LAP, 3cm in diameter
Case 3: 64 y-o male patient. Clinical story: DLBCL 16 years ago involving left parotid gland and palatine tonsilla. 7x5 cm infiltrative mass. Lymphoma recurrence vs salivary gland tumor?
Reactive vs follicular lymphoma
Case 8: 57- y-o female patient with MDS with bilateral supraclavicular pathological LAP FNA from left supraclavicular mass