Extranodal Lymphomas

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How are extranodal lymphomas different?

- Many represent extranodal presentations of systemic disease
- Some are unique to specific anatomic sites
- One-third of malignant lymphoma cases present as extranodal disease
- Often small and fragmented biopsies
- Lack of normal nodal architecture makes the cases more challenging
- Differential diagnosis is more often with reactive lymphoid infiltrates compared to nodal disease

Anatomic Site

Importance of Anatomic Site in Diagnosing Extranodal Lymphoma

- Some lymphoma types primarily involve extranodal sites, sometimes with fairly unique clinical features
  - Burkitt lymphoma
  - Nasal type, extranodal NK/T cell lymphoma
  - Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT)
  - Hepatosplenic T cell lymphoma
- Biopsy site and clinical information are important!
- Remember that systemic disease involving an extranodal site is often more common than primary extranodal disease
How to Approach Extranodal Lymphoid Proliferations

- Morphology
- Immunophenotype
- Selected molecular genetic testing
- Clinical correlation

Morphology

- Sheets of large cells
- Sheets of small cells
- Mixture of cell types
- Presence of nodules and/or germinal centers

Sheets of Large Cells

- Usually supports lymphoma,
- Except in small biopsies
  - exclude a reactive germinal center
  - CD10, CD21, BCL2
  - Levels

Primary DLBCL of the CNS
ALK+ Anaplastic Large Cell Lymphoma

Intravascular Large B-Cell Lymphoma

Florid Follicular Hyperplasia

Burkitt Lymphoma

Florid Reactive Follicular Hyperplasia
Sheets of Small Cells

- Worrisome features
  - Monotonous
  - Dense and infiltrative
  - Paratrabecular marrow pattern

- Less worrisome
  - Admixed neutrophils
  - Adjacent to an area of infection or trauma

Mantle Cell Lymphoma

Extranodal Marginal Zone Lymphoma

- Breast

Extranodal Marginal Zone Lymphoma

- Salivary Gland
Epithelial Invasion

Paratrabecular Lymphoid Aggregates in the Bone Marrow

CD20

CD3
Mixture of Cells Types

- Heterogeneous lymphocytes with plasma cells
  - May still be clonal, check plasma cell clonality
- Lymphoid cells with epithelioid histiocytes
  - Not helpful, could still represent lymphoma, especially mantle cell lymphoma, or lymphoplasmacytic lymphoma
- Monocytoid B cells with admixed neutrophils
  - Usually a reactive pattern

Heterogeneous Cell Populations

- Subcutaneous Panniculitis-like T-cell Lymphoma
- Angioimmunoblastic T-cell Lymphoma
- Thymic Extranodal Marginal Zone Lymphoma
Epithelioid Histiocytes

Monocytoid B-cells

Reactive (Toxo)

Mantle Cell Lymphoma

ENMZL

Reactive (Toxo)
Presence of Nodules and/or Germinal Centers

- Are they neoplastic nodules (lymphoma) or reactive germinal centers?
- If they are reactive germinal centers:
  - The presence of reactive germinal centers does not prove that the surrounding lymphoid infiltrate is benign
    - Common in extranodal marginal zone lymphomas
    - May also occur mantle cell lymphoma
Immunophenotype

- Immunophenotyping is essential in the evaluation of all possible extranodal lymphomas
  - Light chain clonality
  - Assessment of normal immunoarchitecture
  - Aberrant antigen expression
  - Aberrant oncogene expression

Light Chain Clonality

- Usually a good indicator of lymphoma
- Exceptions
  - HHV8-associated Castleman’s disease
  - Marginal zone hyperplasia of GI tract in children
- Monotypic plasma cells may also occur in neoplastic T cell proliferations
  - Angioimmunoblastic T cell lymphoma
  - Peripheral T cell lymphoma, NOS

Light Chain Clonality

- Kappa
- Lambda
Angioimmunoblastic T-cell Lymphoma

Immunoarchitecture

- T and B lymphocytes typically retain their immunoarchitecture in extranodal sites
  - B cells remain associated with follicular dendritic cell networks
  - B cells do not infiltrate in sheets outside of networks
  - B cells do not invade epithelium
- Too many B cells and B cells where they do not belong should raise suspicion for lymphoma

Light Chain Clonality

Kappa
Lambda

Immunoarchitecture

CD3
CD20
BCL2

CD20
CD21
Lymphoepithelial Lesions

B-cells Invading Epithelium

Keratin

CD20

CD79a

CD21

CD20 Gastric MALT

CD20 Salivary Gland MALT
Sialadenitis

Aberrant Antigen Expression

- **B cells**
  - Aberrant CD5 or CD43 expression
  - BCL2 expression by monocytoid B-cells
  - CD10 in B cells outside of follicles
- **T cells**
  - Loss of CD2, CD3, CD5
  - Expression of CD10 on T cell outside of follicles
Aberrant Antigen Expression
Gastric Extranodal Marginal Zone Lymphoma
CD20  CD43  CD5

Aberrant Antigen Expression
BCL2-positive Monocytoid B-cells In Salivary Gland Marginal Zone Lymphoma

CD10+ Lymphocytes Outside of Follicles
Marginal Zone Lymphoma Colonized Follicles
Follicular Lymphoma Interfollicular Involvement
Angioimmunoblastic T-cell Lymphoma CD10+ T-cells

Aberrant Antigen Expression
Subcutaneous Panniculitis-like T-cell Lymphoma
CD2  CD5  CD7
Aberrant Oncogene Expression

• B cells
  – Cyclin D1 (BCL1)
  – BCL2
    • Only useful in follicles
• T cells
  – ALK1
  – TCL1

Oncogene Expression on B-cells

BCL2 in Mantle Cell Lymphoma
BCL2 in Follicular Lymphoma
Cyclin D1 (BCL1) in Mantle Cell Lymphoma

Oncogene Expression on T-cells

ALK-positive Anaplastic Large Cell Lymphoma of the Intestine

Molecular Genetics

• Commonly used to evaluate extranodal lymphoid proliferations
• Most useful to address the question of “reactive versus neoplastic”
• Can also be useful
  – For lymphoma subtyping
  – For lymphoma prognosis
• Think before you order these tests
Molecular Genetic Assessment of Reactive versus Neoplastic

- Assessment of antigen receptors is most useful in this situation
  - B lineage
    - *IGH@*
    - *IGK@
  - T lineage
    - *TRG@
    - *TRB@
- May also use selected translocation testing in some cases
  - *IGH@/BCL2*

Molecular Genetics in Lymphoma Subtyping

- Usually not necessary
- Most common targets
  - t(14;18)(q32;q21); *IGH@/BCL2*
    - Follicular lymphoma, some diffuse large B cell lymphoma
  - t(11;14)(q13;q32); *IGH@/BCL1*
    - Mantle cell lymphoma, some cases of multiple myeloma
  - t(8;14)(q24;q32); *IGH@/MYC* and variants
    - Burkitt lymphoma, and some diffuse large B cell lymphoma
  - t(2;5)(p23;q35); *NPM1/ALK* and variants
    - Anaplastic large cell lymphoma
    - ALK1 immunohistochemistry usually sufficient

Molecular Genetics in Lymphoma Prognosis

- Usually not necessary
- Gastric marginal zone lymphoma
  - Cases with t(11;18)(q21;q21) do not respond to *H. pylori* therapy
- Identification of "double hit" lymphomas
  - Large B cell proliferations with *MYC* and either *BCL2* or *BCL6* translocations are more aggressive

Gene Rearrangement Studies Expected Results

- Negative
- Positive
Gene Rearrangement Studies
Unexpected Results

Peripheral Blood from a Healthy Donor

Gene Rearrangement Studies
Unexpected Results

Peripheral Blood from a Healthy Donor

Gene Rearrangement Studies
Unexpected Results

Gene Rearrangement Studies
Unexpected Results

Unremarkable pelvic node from a radical prostatectomy specimen in a 50 year old man
What to think about before ordering molecular genetic tests

• Are there enough B or T lymphocytes in the sample for me to really be worried about lymphoma?
• What will I do with a positive (or negative) molecular genetic result in this case?
• Would another test or a another biopsy be more useful than molecular genetic studies?

Summary

• Clinical information, including disease presentation and history of lymphoma are essential in diagnosing extranodal lymphoid proliferations
• Immunophenotyping is required for essentially all cases with atypical morphologic features
• If there are TOO MANY B CELLS, be worried and do more
• Understand how you will use molecular genetic tests before you order them
• Don’t be afraid to ask for more tissue

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