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Nodal Marginal Zone B-cell Lymphoma and Its Differential Diagnosis: A Perspective of A Diagnostic Pathologist

Outline of my Presentation Today

- Introduction
- Illustrating, naming and defining spherical/ball-Like structures to identify benign diseases & lymphoma
- Normal marginal zone in spleen, peyers patches, nodes
- Difference between marginal zone & monocytoid B-cells
- Definition, histologic & immunophenotpe of Nodal marginal zone lymphoma (NMZL)
- Differential diagnosis of marginal zone pattern:
  - Benign
  - B-cell lymphoma
  - T-cell lymphoma, Mast cell disease, other diseases
- Summary

Introduction

- Fundamental Importance of Histology
- Lessons Learned from Experience
- Diagnostic Approach i Practice & Preach

Fundamental Importance of Histology

- As a independent method, histologic evaluation provides many types of specific diagnostic information that is NOT obtained by any other method, and without histological evaluation, accurate diagnosis cannot be made
- Histologically, most pathologic processes form in one or more nodal compartments, distinctive abnormalities that are usually labeled as patterns

-A narrow histological differential diagnosis is the most important first step in making accurate diagnosis, and it drives all other studies that need to be done to reach a final accurate diagnosis

Lessons Learned from Experience (1of 2)

- We don't know what we don't know
- We see under the microscope (recognize) what we know

  All recognition is done by the mind and none by the eyes. Thus, if the mind does not know, we cannot recognize what is present and therein lie the dangers of making wrong diagnosis
- In order to recognize microscopic images instantly and accurately, we must see them slowly, critically & repeatedly (> 100 times) *so that they are permanently imprinted in the mind for instant accurate recall, when encountered in the future*
- The more we know, the more we see (recognize) (due to acquired experience & knowledge)

6

Lessons Learned From Experience (2 of 2)

- What we see is also greatly influenced by OUR:
  1. concepts about pathogenesis of lymphoid diseases
  2. histologic, immunophenotypic & other criteria we use in our daily practice to reach a final diagnosis
  3. the approach & the methods we use in our diagnostic practice to detect pathologic areas, & also the problem solving strategies we use to resolve a differential diagnosis
- Making histologic diagnosis & interpreting immunohistochemical stains and integrating these with clinical & other information is an ART and NOT a SCIENCE

Introduction: Diagnostic Approach I Practice & Preach

- -Review of all H&E stained slides without ANY clinical history
- -Carefully review histologic features, at low and high magnification, & note the most important findings
- -Form a narrow, well thought out differential diagnosis (DDX) based on histological features
- -Read the clinical history and revise the DDX
- -Order immunostains to narrow the DDX
- -Form a revised DDX
- -Order molecular & other studies/tests if needed, and also for clinical and prognostic reasons
- -Form a final DDX that you can justify and defend

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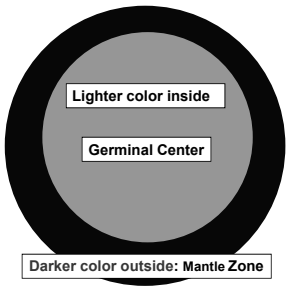
Illustrating, Naming and Defining Spherical/Ball-Like Structures to Facilitate Accurate Recognition of Pathologic Processes, Benign Diseases and (Marginal Zone) Lymphomas

10

Spherical Ball-like Structures (Patterns) Seen in Lymph Nodes

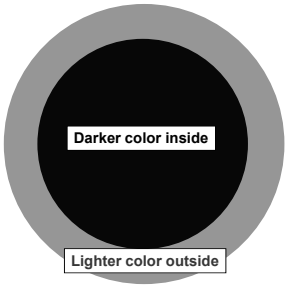
1. Follicular pattern
2. Mantle zone pattern
3. Mantle cell nodular pattern
3. Marginal zone pattern
5. Marginal zone nodular pattern
6. Follicular colonization pattern
7. Inverse follicular pattern
8. Progressively transformed germinal centers (PTGC)
9. L&H nodules
10. "Proliferation Centers"
11. Paracortical nodular T-zone hyperplasia
12. Fibrous nodular

NORMAL ARRANGEMENT OF COLORS IN A TYPICAL FOLLICLE, AT LOW MAGNIFICATION

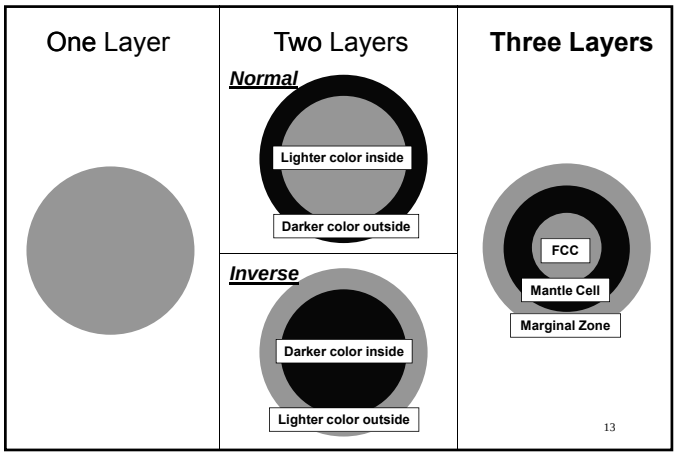


FOLLICULAR PATTERN

INVERSE ARRANGEMENT OF COLORS IN A FOLLICLE, AT LOW MAGNIFICATION



INVERSE FOLLICULAR PATTERN



Frequency of Presenc of Benign Marginal Zones :

- **Normal spleen in almost all cases**
- **Peyers patches in all cases**
- **Mesenteric lymph nodes common**
- **Peripheral lymph nodes rarely**
- **Marginal zone hyperplasia with clear cytoplasm**

MARGINAL ZONE PATTERN IN NORMAL PEYERS PATCHES OF SMALL INTESTINE

FOCAL, SUBTLE MARGINAL ZONE PATTERN IN BENIGN MESENTRIC LYMPH NODE

COMPLETE & WELL DEFINED MARGINAL ZONE PATTERN IN BENIGN MESENTRIC LYMPH NODE

PARTIAL MARGINAL ZONE PATTERN IN BENIGN PERIPHERAL LYMPH NODE

MARGINAL ZONE B-CELL HYERPLASIA WITH CLEAR CYTOPLASM IN PERIPHERAL LYMPH NODE

Marginal Zone B-cells Are Different From Benign Monocytoid B-cells Seen In Peripheral Nodes

Benign Monocytoid B-cells

21

Lymph Nodes With BENIGN Monocytoid B-Cells (MBC)

First described by Professor A. G. Stansfeld in 1961

- **Always seen in Toxoplasmosis (most common parasitic infection in US), and in Brucellosis**
- **HIV infection, in early stages, clusters of MBC present in ~95% of cases**
- **Sometimes in viral infections, cat scratch disease, other lymphadenitis. Overall, monocytoid B-cell clusters are rarely seen in lymph nodes**

Occurrence: Almost always in the form of, one to multiple, clusters of variable size

Location of Monocytoid B-cells: In the sinuses in >95 of cases (subcapapsular, trabecular, interfollicular), adjacent to follicles, and interfollicular areas; rarely partially or completely surround benign follicles and thus may form a marginal pattern (HIV infection).

Cytological features: typically medium size lymphoid cells with open chromatin structure, indistinct to small nucleoli and moderate to abundant pale to clear cytoplasm. Admixed variable #s of neutrophils

Immunophenotype: Positive: CD20, T-bet, IRTA-1, Bcl-2 (10% of cases)

Negative: CD27, CD5, CD23, IgD, IgM, CD43

MONOCYTOID B-CELL CLUSTERS IN TOXOPLASMOSIS

23

NECK NODE IN A HIV + PATIENT:

Benign Monocytoid B-cells Produce Partial Marginal Zone and Inverse Follicular Patterns

Terminology and Classification of Marginal Zone Lymphomas

The Term Marginal Zone Lymphoma is Employed for Different Types of Lymphomas

- -Splenic B-cell marginal zone B-cell lymphoma (SMZL)
- -Extranodal marginal zone B-cell lymphoma of mucosa associated lymphoid tissue (MALT), type
- -Lymph nodes with marginal zone lymphoma
- (Primary) Nodal marginal zone B-cell lymphoma (NMZL)

Nodal Marginal Zone Lymphoma (NMZL): Definition

- ***-A primary nodal B-cell neoplasm that morphologically resembles lymph nodes involved by MZL at extranodal sites or in spleen, but without evidence of extranodal or splenic disease*** **(WHO 2008)**
- -Integration of clinical and pathologic data is required to make the diagnosis on NMZL
- -No concurrent lymphoma. No lymphoma at staging in extranodal site or in spleen, or splenomegaly
- -No prior history of lymphoma. However, if history of lymphoma, review of these original biopsy slides is necessary to verify accuracy

Epidemiology

- **NMZL accounting for 1.5-1.8% of lymphoid neoplasms**
- **The incidence appears to be increasing most likely due to a "real" increase, rather than better recognition**
- **Median age is 60 (ranges from adolescence to >90y)**
- **Sex: M:F is 1:1**

Cell of Origin

- -From mature B-cells with rearranged immunoglobulin genes
- -However, the precise origin remains poorly defined
- -Somatic hypermutation (SHM) is present in ~85% - suggesting post-GC cell origin
  - –However, <50% showed evidence of antigen selection
  - –There is an accumulating evidence for GC-independent SHM
  - –One study suggests derivation from GC B cells (Conconi, Blood 2001)

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Clinical and Laboratory Features of Patients with NMZL

- LDH is elevated in 12-48%
- B2-microglobulin is increased in 29-45%
- M-component in present in 6-33%
- Cryoglobulins in one study in 14% (2/14)
- Hypogammaglobulinemia in 7-10%

The clinical presentation is non-specific and highly variable

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MORPHOLOGY OF NODAL MZL

- Non-neoplastic component
- Neoplastic component
  - –Patterns
  - –Cytology
  - –Transformation
  - –Differential Diagnosis

NMZL: NON-NEOPLASTIC COMPONENT

- Benign component is often multifocal, ***prominent or predominant***:
  - *Reactive follicles seen in >90% of cases*
    - Few to predominating
    - Atrophic or hyperplastic
    - With or without mantle zones

    -Reactive follicles may focally or partially or completely colonized by marginal zone B-cells

    -Polyclonal plasma cells must be distinguished from monotypic plasma cells

Morphology of Nodal Marginal zone Lymphoma

- -Non-neoplastic component
- -Neoplastic component
  - – Multiple patterns present
  - – Spectrum in cytologic features
    - -Marginal zone B-cells
    - -Plasmacytoid forms
  - – Transformation Criteria
  - –Differential Diagnosis

Nodal Patterns Seen in Marginal Zone B-cell Lymphoma

- -Marginal zone &/or inverse follicular in 75%
- -Follicular colonization pattern in 65%
- - Sinus pattern in 35%
- - Interfollicular pattern in 35%
- -Combination of the above patterns in 90%
- -Completely diffuse pattern is rare (<10%)

Gastric MALT Lymphoma
Involving Perigastric Node

Focal

Marginal Zone and Inverse Follicular Patterns

Neck Node:

Complete Marginal Zone Pattern,
With
Thin Marginal Zones

Neck Node:

**Complete Marginal Zone Pattern,
With
Thick Marginal Zones**

NODE WITH:

**PROMINENT
INVERSE FOLLICULAR PATTERN**

Node With Multiple Paterns:

- **Marginal Zone**
- **Inverse Follicular**
- **Marginal Cell Nodular**
- **Confluence Of Adjacent Marginal Zones**

Node:

Sinusoidal & Parasinusoidal

Pattern

Lymph Node:

**Confluent
Interfollicular Pattern**

Follicular Colonization Pattern

Stomach MALT Lymphoma
with
Follicular Colonization

Node: Follicular Colonization

Follicular Colonization
By
Marginal Zone B-cells & with
Plasmacytic Differrention
in
Follicles and/or in Interfollicular areas

Follicular Colonization
By
Marginal Zone B-cells
&
with
Plasmacytic Differentiaton
in
Interfollicular areas

Marginal Zone B-cell Lymphoma
with
Plasmacytic Differentiation
In
Interfollicular Areas

Plasmacytic Differentiation
In
Interfollicular Areas
With Russell Bodies

CYTOLOGIC FEATURES of MZL

Cytological Spectrum:

- **Size: small to medium**
- **Nucleus slightly irregular, nucleoli not prominent**
- **Cytoplasm: scanty to abundant, pale to lightly eosinophilic**
- **Monoclonal plasma cells and plasmacytoid forms in 35%**
- **Scattered malignant transformed cells**

TRANSFORMATION

Histologic Criteria:

- **Monomorphic clusters &/or islands of large cells or sheet of large cells**
- **> 50% large cells that are not in clusters and/or islands ??**

A Case with Focal transformation

NMZL

No specific Immunohistochemical, Cytogenetic or Molecular Biomarkers have been Established

Immunophenotype of NMZL:

- **NMZL cells are positive:**
  - **CD20, CD79a, and PAX5**
  - **BCL2 in 43-100%; MUM1 majority**
  - **CD43 in 5-75%, CD23 in 0-29%**
  - **CD5 in 0-17%**
  - **CD10 rarely**
  - **MNDA in 75% in NMZL and 5% in FL**
  - **IRTA1 (immunoglobulin superfamily receptor translocation-associated 1) in 73% of NMZL and 0 in 320 FL**

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NMZL:Conventional Cytogenetics & FISH

- **Numerous cytogenetic abnormalities have been reported**
- **NO specific alterations have been identified so far**
- **Multiple translocations have been reported, but they do NOT share a common breakpoint region**

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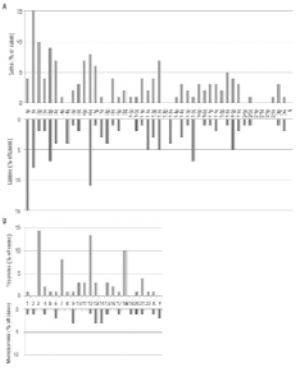
Classical Cytogenetics & FISH in NMZL

- -Consistent cytogenetic aberrations have NOT been identified
- Numerical abnormalities involving chr 3, 7, 12 and 18 are MOST common



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van den Brand & van Krieken Haematologica 2013;98:1003-1013

Molecular Features of NMZL

- Increased expression of MNDA
- Mutations leading to activation of NF-kB pathway
  - Overexpression of NF-kB-related genes (TRAF4,CD82)
  - Inactivating mutations of TNFAIP3, an inhibitor of the NF-kB pathway in 3/9 cases of NMZL
- Increased expression of IL-32, histones, members of TNF family (TACI, TNFRSF14)
- Increased expression of microRNA: miR-224, miR-223, & let-7f

van den Brand & van Krieken Haematologica 2013;98:1003-1013

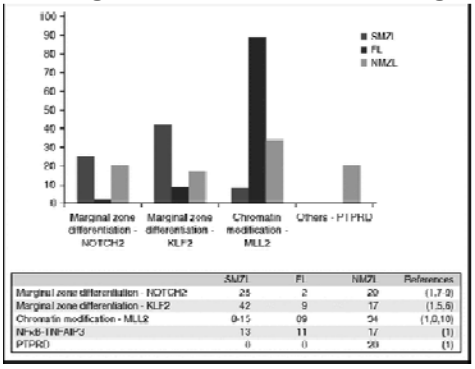
REFERENCES

1. M A Piris. Nodal Marginal Zone Mutational Signature. Commentary: Blood. 2016; 128: 1315-1316
2. Spina V et al. The Genetics of Nodal Marginal zone Lymphoma. Blood. 2016; 128: 1362-1373

- PTPRD lesions are among the most recurrent alterations in NMZL and appear to be enriched in this lymphoma type across mature B-cell tumors.

- NMZL and SMZL genetics overlap with the exceptions of PTPRD lesions, supporting their distinction as independent entities

Nodal Marginal Zone Mutational Signature



	SMZL	FL	NMZL	References
Marginal zone differentiation - NOTCH2	25	2	20	(1,7,9)
Marginal zone differentiation - KLF2	42	9	17	(1,5,6)
Chromatin modification - MLL2	9-15	09	34	(1,9,10)
NFκB-TNFAIP3	13	11	17	(1)
PTPRD	0	0	50	(1)

Nodal Marginal Zone Mutational Signature. Commentary: Blood. 2016; 128: 1315

Differential Diagnosis Of Marginal Zone Pattern and Nodal MZL

Dictionary Definition of the Word "Marginal"

- Constituting a margin
- Borderline
- Border
- Edge
- Being adjacent

Formation of Marginal Zone Pattern in the Lymph Node

- In the node, the marginal zone is a border between B-cell and the T-cell compartments.

- At this border, many different cell types may be found that include: B-cells, T-cells, plasma cells, mast cells, etc.

Reasons for Showing The Differential Diagnosis of The Marginal Zone and/or the Inverse Follicular Patterns

1. **> 99% of pathologists, when they see the above patterns, they make a diagnosis of a Marginal Zone B-cell Lymphoma (MZL), because they consider these patterns as being specific for MZL.**
2. **However, the above patterns are absent in 25% of MZL.**
3. **Also, marginal zone and inverse follicular patterns are present in benign diseases, other B-cell, & T-cell lymphomas, and other diseases (<u>next slide</u>). These diseases will be shown today.**
4. **Some cases reported in the literature as MZL with an aberrant phenotype (CD5+, CD23+ Cyclin D1+, CD10+) are NOT MZL, but examples of the above diseases producing these patterns.**

Differential Diagnosis – Marginal zone / Inverse Follicular Pattern

Benign	B Lymphomas	T Lymphomas	Other
Spleen	SLL/CLL	PTCL, Perifollicular	Mastocytosis
Peyer's Patches	Mantle Cell	Angioimmunoblastic T- cell Lymphoma (AITL)	
Mesenteric Node	FL with Inverse follicular pattern		
Peripheral Node	FL with MZB differentiation		
Monocytoid B-cell Hyperplasia	FL with MZB & Plasmacytic differentiation		
Marginal zone B-cell Hyperplasia			

Atypical
Autoimmune Lymphoproliferative Syndrome (ALPS)

Follicular Lymphoma, Grade 2/3
with
Inverse Follicular Pattern
Produced by
Small and Large Centroblasts
in the
Periphery of the Follicles

Follicular Lymphoma
With
Marginal Zone B-cell Differentiation
Producing
An Inverse Follicular Pattern

Follicular Lymphoma with
Marginal Zone B-cell Differentiation
and
with
Follicular Colonization

Follicular Lymphoma With
Marginal B-cell & Plasmacytic
Differentiation
Producing
A Marginal Zone Pattern

Small Lymphocytic Lymphoma (CLL)
With
Marginal Zone Pattern

Small Lymphocytic Lymphoma (CLL)
With
Marginal Zone Pattern

Mantle Cell Lymphoma
With Inverse Follicular Pattern & With
Clear Cytoplasm
Mimicking A Marginal Zone Lymphoma

Angioimmunoblastic T-Cell Lymphoma
With
Marginal Zone Pattern

Angioimmunoblastic
T-cell Lymphoma
With
Marginal Zone Pattern

Autoimmune Lymphoproliferative Syndrome (ALPS)

Mast Cell Disease Producing

Inverse Follicular Patterns

Metastatic Carcinoma

Summary of Nodal Marginal Zone Lymphoma

- **-Criteria for making diagnisis of Nodal MZL, by definition, are that it has to be a primary in the node, and NO prior or concurrent evidence of MALT or Splenic MZL**
- **-No specific immunohistochemical, cytogenetic or molecular biomarkers have been established for NMZL**
- **- Nevertheless, histologic features, immunostains, and judicious use of other studies establish the diagnosis of NMZL**
- **- Also, newer markers can be useful to distinguish NMZL from Follicular Lymphoma, but additional studies need to be done to confirm their value:**
  - **- MNDA is positive in 75% in NMZL and 5% of FL;**
  - **- IRTA1 is positive in 73% of NMZL and 0% of FL**

Understanding The Phenomenon of:

"The Mind Closes The Gaps In Knowledge While Making Decisions (And Its Consequences)"

76

The Mind Closes the Gaps in Knowledge During the Diagnostic Process (3 of 4)

- **Gaps in Knowledge: Images, criteria of diseases & histologic features, & about pathogenic mechanisms of diseases**
- **The mind does not know what it does not know (the gaps in its own knowledge necessary to make accurate diagnoses)**
- **The gaps in knowledge are completely ignored by the mind (unknowingly and automatically) while making a diagnosis or decisions**

77

The Mind Closes the Gaps in Knowledge During the Diagnostic Process (4 of 4)

- **Thus, the mind takes into consideration during the decision making process, ONLY what it knows or has recognized (images)**
- **In other words, the mind automatically ignores (closes) the gaps in its knowledge without realizing it. Unfortunately, the mind intuitively thinks it has sufficient knowledge to make diagnosis**
- **Thus, there is no substitute to rigorous training, and experience**

78

THANK YOU