Neoplastic Disorders of the Spleen
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Indiana University School of Medicine

Introduction and Overview of Normal Splenic Anatomy and Function
Attilio Orazi

The spleen: gross anatomy
- Bean shaped organ
- Weights 50-250g (median 150g)
- Decreases with age
- Covered by peritoneum
- Often fibrotic plaques (can be calcified)
- Capsule devoid of muscle fibers

Compartments:

White pulp
- Follicles (Malpighian bodies), 1-2 mm nodules
- PALS*
  - Function: immunologic

Red pulp
(75% of the spleen volume)
- Cords of Billroth
- Sinuses
  - Function: filtering

*Peri-Arteriolar Lymphoid Sheets

Under the microscope

PAS stain: basement membrane hoops
Splenic Functions

I. Filtration
   A. Culling - erythrocyte (or other blood cell) destruction
      1. Physiologic (as red blood cells age)
      2. Pathologic
         a. Associated with blood cell abnormalities
         b. Associated with primary splenic changes
   B. Pitting (facelifting) of erythrocytes
      1. Removal of cytoplasmic inclusions
      2. Remodeling of cell membranes
   C. Erythroclasis - destruction of abnormal erythrocytes
      with liberation into circulation of their fragments
   D. Removal of other particulate material (e.g., bacteria,
      colloidal particles)

II. Immunologic
    A. Trapping and processing of antigen
    B. “Homing” of lymphocytes
    C. Lymphocyte transformation and proliferation
    D. Antibody and lymphokine production
    E. Macrophage activation

III. Reservoir
    A. Storage of platelets and granulocytes
    B. Recycling of iron
    C. Red blood cell storage (minor in humans)

IV. Hematopoietic
    A. Erythropoiesis, granulopoiesis, megakaryopoiesis
       (not a normal function in fetal or adult spleens)
    B. Lymphocyte and macrophage production

Splenic Histology and Immunohistochemical Evaluation

J. Han, J. M. van Krieken, and Attilio Orazi
In “Histology for Pathologists, Third Edition”, Edited by Stephen S.

Stroma matrix:

- Reticulin
- Collagen IV
- Non-specific - pan collagen
- Basal membrane collagen - ring fibers

Adventitial reticulum cells:

- NGFR (Me20.4)
- Spindle cells with structural functions, DRCs

Litoral cells:

- CD8, CD68, CD21
- Lining cells of splenic sinuses
- VWF/CD31/CD34
- Similar to other endothelia

Macrophages:

- CD68 (PG-M1)
- Cordal macrophages and monocytes

Myoid cells:

- SMA
- Pericytes and perifollicular cells

Red Pulp: vascular structures and cord macrophages

- Litoral cells
  - VWF, CD31, CD8, CD68; (CD34 neg.)

- Other endothelia
  - VWF, CD31, CD34; (CD68, CD8 neg.)

- Cordal Macrophages
  - CD68
White pulp: composition

- **Follicles**
  - i. Primary
  - ii. Secondary (tripartite follicle)
- **PALS**
  (Paratrabecular lymphoid sheaths)

White pulp immunohistochemistry

- **GERMINAL CENTERS**
  Follicular dendritic cells: CD21, CD23, CD35, NGFR
  B-cells: CD20, CD19, high Mb-1, BCL-2 neg.; T-cells: CD3
- **MANTLE ZONES**
  IgM, DBA.44, CD23+, low Mb-1
- **MARGINAL ZONES**
  IgM, (IgD +/−), IRTA-1
- **PALS**
  CD4:CD8 = 3:1, rare IB (high CD30 pos.), IDCs: S100+

General Considerations on the Diagnosis of Splenic Disorders

Attilio Orazi

Gross Pattern

**Diffuse splenic enlargement**
- White pulp: subtypes of lymphoid neoplasms vs. reactive lymphoid hyperplasia
- Red pulp: subtypes of lymphoid neoplasms vs. leukemic infiltration vs. reactive proliferations (e.g. histiocytosis)

**Focal splenic pathology**
- Large cell lymphomas & Hodgkin vs. pseudo-neoplastic lesions (e.g. IPT) or non-hematopoietic tumors (e.g. vascular)

Diffuse: all organ is involved

- **White pulp:**
  - small B-cell lymphomas (e.g. SMZL) vs. lymphoid hyperplasia
- **Red pulp:**
  - leukemias (e.g. CML) vs. subtypes of lymphoid neoplasms vs. reactive conditions

Focal splenic pathology

- Large cell lymphomas and Hodgkin disease
- Pseudo-neoplastic lesions (e.g. IPT)
- Non-hematopoietic tumors (e.g. vascular, metastatic)
Lymphoid Hyperplasias

Dennis P. O’Malley

Splenic Hyperplasia Overview

- Follicular hyperplasia
- Marginal zone hyperplasia
- T-cell hyperplasia

Splenic Hyperplasia

Follicular

Typical Follicular Hyperplasia
- Similar to lymph node
- Similar histology
- Similar criteria for b9 versus lymphoma
- CLINICAL: many etiologies including infectious and autoimmune
- DIFFERENTIAL DIAGNOSIS: follicular lymphoma, other B-cell/white pulp lymphomas

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Follicular Lymphoma</th>
<th>Follicular Hyperplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in follicle density</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Lack of tingible-body macrophages</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Mantle zone</td>
<td>Poorly formed or absent</td>
<td>Present</td>
</tr>
<tr>
<td>Follicle polarization</td>
<td>Not present</td>
<td>Often present</td>
</tr>
<tr>
<td>Dysplastic/abnormal cytology</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Ki67 proliferation rate</td>
<td>Low</td>
<td>High</td>
</tr>
</tbody>
</table>

Follicular Hyperplasia: Tingible-body macrophages

Follicular Hyperplasia: H&E

Follicular Hyperplasia: Ki67

Follicular Lymphoma: H&E

Follicular Lymphoma: Ki67

FL: H&E

FL: Ki67
Splenic Hyperplasia

Follicular

Localized (nodular) reactive lymphoid hyperplasia

- Grossly visible nodule(s)
- Clusters of benign follicles
- Lack features of neoplastic follicles
- CLINICAL: etiology unknown, possibly similar reactive conditions to usual hyperplasia

Primary follicles:

- Composed of mantle cells
- Either immunologically unchallenged spleen (children)
- OR secondary immune suppression – STEROIDS!
- May mimic mantle cell lymphomas or other small B-cell lymphomas

Marginal Zone

Expansion of the outer (third) layer of splenic follicle structure

- CLINICAL: variety of causes
  - Notably autoimmune phenomenon (ex. ITP, autoimmune hemolytic anemias)

Cytology

- Small lymphocytes with increased cytoplasm
- Occasional plasma cells or plasmacytoid lymphocytes (Russell bodies, Dutcher bodies rare)
- Occasional larger, transformed cells

Hyperplasia defined as increased of layer thickness to >12 cells*


Splenic Hyperplasia
Marginal Zone

Differential diagnosis:
- Marginal zone lymphoma!
- Other small B-cell/white pulp lymphomas

<table>
<thead>
<tr>
<th>Features</th>
<th>MZH</th>
<th>MZL</th>
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</thead>
<tbody>
<tr>
<td>Expanded MZ (&gt;12 cell layers)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Numerous B-cells in PALS</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Follicles</td>
<td>3 layers</td>
<td>Loss of layers; often uniform single layer</td>
</tr>
<tr>
<td>Red Pulp</td>
<td>No increase in red pulp B-cells</td>
<td>Often has clusters of red pulp B-cells</td>
</tr>
<tr>
<td>Clonality</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Kappa/lambda</td>
<td>Polyclonal</td>
<td>Monoclonal</td>
</tr>
<tr>
<td>Ki67</td>
<td>Normal secondary follicles with high proliferation</td>
<td>Colonized follicles have low proliferation in neoplastic cells</td>
</tr>
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</table>

**Hyperplasias and Neoplastic Differential Diagnosis**

<table>
<thead>
<tr>
<th>Hyperplasia</th>
<th>Follicular lymphoma</th>
</tr>
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<tbody>
<tr>
<td>Follicular Hyperplasia</td>
<td>Mantle cell lymphoma</td>
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<tr>
<td>Small lymphocytic hyperplasia</td>
<td>Marginal zone lymphoma</td>
</tr>
<tr>
<td>Immunoblastic hyperplasia</td>
<td>CLL/SLL</td>
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<tr>
<td>Immunoblastic hyperplasia</td>
<td>LGL</td>
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<tr>
<td>Immunoblastic hyperplasia</td>
<td>Hairy cell leukemia</td>
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<tr>
<td>Immunoblastic hyperplasia</td>
<td>DLBL</td>
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<tr>
<td>Immunoblastic hyperplasia</td>
<td>Hodgkin lymphoma</td>
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<tr>
<td>Immunoblastic hyperplasia</td>
<td>Malignant histiocytosis</td>
</tr>
<tr>
<td>Immunoblastic hyperplasia</td>
<td>Langerhans cell histiocytosis</td>
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<tr>
<td>Immunoblastic hyperplasia</td>
<td>Blastic leukemia</td>
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**Splenic Hyperplasia**

T-cell Hyperplasia

Immunoblastic
- Most often viral-related
- Prototype is acute EBV infection
- Increase in immunoblasts in white pulp
- May show invasion of vessel walls and trabeculae

**DIFFERENTIAL DIAGNOSIS:** large cell lymphomas, cHL, histiocytic disorders

IHC, flow and molecular studies can be helpful

Adapted from: Burke. AJCP 1993;99(4).
Acute EBV: immunoblastic reaction

Acute EBV: vasculitis

Splenic Hyperplasia

T-cell Hyperplasia

ETIOLOGY: viral infection, immunodeficiency, drug reactions

DIFFERENTIAL: T-cell lymphomas (esp. LGL), flow or molecular studies are helpful

T-cell hyperplasia: CVID

24 year-old woman
Frequent infections
History of common variable immunodeficiency
Asymptomatic splenomegaly
Lymphoid Neoplasms of the Spleen

Attilio Orazi

Splenic Lymphoid Neoplasms: Three Settings

- **True primary splenic lymphoma**: the tumor is confined to the spleen or splenic hilar lymph nodes, without involvement of other sites
- **Secondary splenic lymphoma**: the spleen is involved as part of a generalized lymphoma spread
- **Lymphomas with prominent and/or predominant splenomegaly**

Secondary Splenic Lymphomas

i. Hodgkin Lymphoma
ii. Non Hodgkin Lymphomas

Staging Splenectomy for Hodgkin Lymphoma

- May be subtle, only a few millimeters in size
- Requires careful sectioning after 24-48 hours fixations of sliced spleen
Hodgkin lymphoma in spleen: microscopic features

- Early lesions: PALS & marginal zones
- As the disease progresses: follicles and red pulp
- Sarcoidal-type granulomas

Criteria for the diagnosis of HL in the spleen

- **Previous diagnosis**
  Abnormally nucleolated large cells (mononuclear variant of Reed-Sternberg cells) within a typical mixed background

- **No previous diagnosis**
  Diagnostic Reed-Sternberg cells must be found or strong immunohistochemical evidence in abnormally nucleolated large cells

Secondarily Involvement by non-Hodgkin lymphoma: B-cell lymphomas

- SLL/CLL: small lymphocytic lymphoma/CLL
- NMZL & LPL: nodal marginal zone lymphoma & lymphoplasmacytic lymphoma
- FL: follicular lymphoma
- MCL: mantle cell lymphoma
- DLBCL: diffuse large B cell lymphoma

Distinction between subtypes of small B-cell lymphomas is difficult

Histologic / cytologic differences, but:

- all may simulate SMZL
- all may infiltrate red pulp

Main Morphologic and Immunophenotypic Differences

- SLL/CLL: monomorphic, rare paraimmunoblasts (CD5+,CD23+)
- NMZL & LPL: monocytoid or plasmacytoid / plasmacytic differentiation (Bcl-6-, CD10-, CD23-, CD5+)
- FL: mixture of centrocytes and centroblasts (Bcl-6+, CD10+)
- MCL: monomorphic (small cell or blastoid) (CD5+,CD23-,Bcl-6-, cyclinD1+)
### CLL/SLL
- Look like primary follicles
- Red pulp infiltration
- Small lymphocytes with prolymphocytes & paraimmunoblasts (no proliferation centers)
- Infiltration of large vessels or trabeculae

### LPL/WM
*LPL/WM*
- Low power similar to CLL/SLL
- Polymorphic infiltrate of lymphocytes, plasmacytoid lymphs, and plasma cells
- Intrasinusoidal BM involvement is less common than in SMZL
- WM*: Monoclonal IgM paraprotein (>3g/dl) with hyperviscosity, anemia, and often bleeding

*Waldenstrom macroglobulinemia

### Cytogenetics/ Molecular Genetics
- Del6q, trisomy 3, 5, 12, 18, monosomy 8.
- t(9;14) very rare (wrongly reported in WHO 2001)
- All LPL IgH mutated with a VH3 predominance

### LPL/WM is a rare disorder!

It should be considered a diagnosis of exclusion after SMZL and plasmacytoid variants of CLL/SLL have been ruled out
Talk with your clinical counterpart: "IgM >3.0g/dl is WM irrespective of morphology"

However, if the clinical-pathologic picture is typical, any level of IgM may go*

Small B cell lymphoma with plasmacytoid (plasmacytic) differentiation


Mantle Cell Lymphoma
- MCL invades and replaces germinal centers, resembles SLL/CLL or SMZL
- Mantle zone pattern rare
- Blastoid variants

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- Mantle zone pattern rare
- Blastoid variants

Follicular Lymphoma (Grade 1)
- Monotonous population of small-cleaved lymphoid cells with inconspicuous nucleoli

Follicular Lymphoma
- Monotonous population of small-cleaved lymphoid cells with inconspicuous nucleoli
- (Grade 1)

Follicular Lymphoma
- Monotonous population of small-cleaved lymphoid cells with inconspicuous nucleoli
- (Grade 2)

Diffuse Large B-cell Lymphoma
- Case #5
- 70 year-old woman presented with fever, night sweats of two weeks; weight loss (15 pounds)

CT and Gross: a 15 cm focal mass in the spleen

Histology:
- lacks predilection for WP
- rare cases show red pulp only involvement
- rare cases show histiocyte-rich and/or
- T-cell rich appearance
Peripheral T-cell lymphomas
- Mycosis fungoides
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma
- PTCL-unclassified
  (incl. lymphoepithelioid/Lennert’s lymphoma)

All PTCL
- Infiltrate and replace the PALS
- Perifollicular tropism
- Variable degrees of red pulp involvement

Selected PTCL
- AILD type: CD10 and EBV
- ALC: CD30, Alk-1
- Cytotoxic subtypes
  - TIA-1, granzyme, perforin

Lymphoid neoplasms with prominent and/or predominant splenomegaly
i. Diffuse White Pulp Enlargement
ii. Diffuse Red Pulp Enlargement
Lymphomas with prominent and/or predominant splenomegaly

**Diffuse White Pulp Enlargement**

**B-cell:**
- Splenic Marginal Zone Lymphoma (SMZL)
- other subtypes

**Diffuse Red Pulp Enlargement**

**T-cell:**
- Hepatosplenic T-cell lymphoma

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Splenomegaly case #2

- 43 year-old male
- Weakness, fatigue, left side pain
- No peripheral adenopathies
- PB smear showed numerous atypical lymphoid cells
- Splenectomy: 2.3 kg. spleen

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Miliary pattern throughout the spleen

**SMZL typical histology**


**SMZL, dimorphic cellular composition**

**SMZL: red pulp granulomas**

CD20
SMZL red pulp: cordal & intravascular involvement

SMZL in transformation

SMZL, indolent variant

Rosso et al. Hum Pathol, 1995

Immunophenotypic and cytogenetic characteristics

<table>
<thead>
<tr>
<th>CD19, CD20, CD22, IgD positive</th>
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<tbody>
<tr>
<td>Allelic loss of 7q21,32 (40%)</td>
</tr>
<tr>
<td>Bcl-6, CD10, CD23, CD43, CD5- ( \cdot ) cyclin D1 IRTA-1 negative</td>
</tr>
<tr>
<td>Trisomy 3 (17%)</td>
</tr>
<tr>
<td>Trisomy 5</td>
</tr>
<tr>
<td>t(11;18)</td>
</tr>
<tr>
<td>t(9;14)</td>
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<tr>
<td>t(11;14)</td>
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<tr>
<td>p53 mutation</td>
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</table>

However CD5, CD10, CD23, CD38 can be rarely positive

SMZL: derivation

- Unmutated immunoglobulin VH genes (30%) naïve B cells or transitional follicular precursor (T2-FP) and marginal zone precursors (T2-MZP)
- Post germinal center origin – somatic hypermutation (70%) memory B cells
  - Ongoing mutations:
    - GC origin for a subset (rare cases CD10 pos. or composite)
    - Alternative B cell diversification pathway (such as in X-linked hyper-IgM syndrome)
- IgH usage in SMZL: VH1,2,4

Etiological associations

- Hepatitis C
- Cryoglobulinemia type II
- Chronic malarial (hyper-reactive malarial splenomegaly, tropical lymphoma)
- Autoimmune disorders
Differential diagnosis: i. reactive conditions

Autoimmune disorders incl. collagen disorders

Immunohistology

CD20 to show subtle infiltration of red pulp:
- Ragged borders
- Clusters
- Intravascular spread

Kappa / lambda stains

Colonization of GC with Bcl-6^neg./ Mib-1low cells

Disruption of DRCs networks

Hilar node examination
Flow cytometry spleen
Cytogenetics
Review of PB smear (villous lymphocytes)
Bone marrow biopsy assessment
Flow on PB and/or marrow
SPEP & UPEP
PCR IgH chain gene

Clonality by PCR IgH V-D-J

Low sensitivity (better with newer techniques)
False positives “when it is needed the most”
Chronic ITP
Lupus
Rheumatoid arthritis

Clonality by Loss of Heterozygosity

LOH can be detected in most cases of myeloid neoplastic disorders of the spleen (using formalin-fixed, paraffin-embedded material)∗

It may be more sensitive and specific than IgH PCR analysis
SMZL: loss of heterozygosity by microsatellite markers for 7q31

Differential diagnosis:
ii. Other small B cell lymphomas

Rarely other hematologic malignancies (e.g. HCL)

SMZL versus other B-cell lymphomas simulating SMZL

- LPL: Alberti & Neiman, Cancer, 1984; Spriano, 1986
- FL: Alkan et al, Hum Pathol, 1996
- B-CLL (rare): Piris et al, Histopathol, 1998
- Blastoid MCL: Mollejo et al, Am J Hematol, 1999

Discussion of Lymphomas Presenting with Prominent Splenomegaly:

SMZL (Bcl-6-, CD10-, CD23-, CD5-) vs. other small cell lymphomas

- LPL: similar dimorphic cellular composition* (Bcl-6-, CD10-, CD23-, CD5-)
- FL: mixture of centrocytes and centroblasts (Bcl-6+, CD10+)
- SLL/CLL: monomorphic, rare paraimmunoblasts (CD5+, CD23+)
- MCL: monomorphic (small cell or blastoid) (CD5+, CD23-, Bcl-6-, cyclinD1+)

*(LPL overlaps SMZL but is WM associated)

SMZL vs. LPL

- The combination of CD25 (WM) and CD22 & CD11c (SMZL) could differentiate between WM and SMZL
- The principal molecular abnormality in WM is 6q deletion (30%), whereas in SMZL the most common abnormalities are loss of 7q (19%) along with +3q (19%) and +5q (10%).

Ocio et al: Clin Lymphoma, 2005

Hepatosplenic T-cell lymphoma case #4

- 24 year-old man came to emergency in acute distress
- Significant hepatosplenomegaly on admission
- PB: severe pancytopenia, otherwise unremarkable.
- Suspected splenic rupture: splenectomy
- Gross: 2,000 gr. spleen with homogeneous red, ‘beefy’ appearance
HSTCL
- CD2, CD3 & TIA-1 positive, CD56+/-
- CD5 negative
- CD4/CD8 double negative
- TCR gamma/delta > alpha-beta
- Isochromosome 7q, +8
- EBV negative
- Post-transplant: several cases reported

HSTCL: Differential Diagnosis
- T-LGL, NK-LGL
- T-ALL / LBL
- Blastic NK-cell lymphoma
- PTCL cytotoxic types
  (CD56 and TIA-1 pos.)
Mature* leukemic B-cell lymphoid neoplasms with prominent and/or predominant splenomegaly

White ± Red Pulp:
- B- prolymphocytic leukemia
- MCL- leukemic with prominent splenomegaly

Red pulp:
- HCL & HCL-variant

*Only exceptionally spleens from patients with pre B-cell ALL are removed - see AML.

Leukemic MCL: descriptions

Hairy cell leukemia case #3
- 43 year-old WM
- Neutropenia and thrombocytopenia
- PB: a few circulating hairy cells
- BMB showed HCL
- Splenectomy performed for massive splenomegaly
- Spleen 3.1 kg with homogeneous red appearance with small hemorrhagic foci (blood lakes)

HCL: splenic histology
- Red pulp
- Blood lakes
- Cords & intravascular Infiltration
- TRAP, DBA.44 immunostaining
Prolymphocytoid variant (classical): 1980
Japanese variant: 1984
Anaplastic variant of HCL: Cancer, 1985
Blastic variant of HCL: Am J Clin Pathol. 1987
HCL with ring-shaped nuclei: Sb Lek. 1991

TRAP pos.

Hairy Cell Leukemia

Differential diagnosis of hairy cell leukemia

SMZL with predominant red pulp / intravascular involvement

Mollejo et al: Histopathology, 2002;40:22

CD10

Systemic Mastocytosis

Tryptase

Mature* leukemic T/NK lymphoid neoplasms with splenomegaly

White and Red Pulp: Red Pulp:
T-PLL (more RP than B-PLL) LGL- T & -NK

*Only exceptionally spleens from patients with T-cell ALL are removed - see AML
Myeloid Neoplasms and Related Disorders

Dennis O’Malley

1. Extramedullary Hematopoiesis
2. Chronic Myeloproliferative Diseases
   1. Essential thrombocythemia
   2. Polycythemia vera
   3. Chronic idiopathic myelofibrosis
   4. Chronic myelogenous leukemia
3. Acute Myeloid Leukemia
4. Systemic Mastocytosis

Extramedullary Hematopoiesis and the Spleen

- Spleen is a frequent site of EMH
- EMH = benign proliferation
  - Very common
- NMP = neoplastic myeloid proliferation
  - Uncommon

Comparison of EMH and NMP

<table>
<thead>
<tr>
<th></th>
<th>EMH (benign)</th>
<th>NMP (neoplastic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilineage or trilineage</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>None</td>
<td>Common</td>
</tr>
<tr>
<td>Abnormal phenotype</td>
<td>Never</td>
<td>Common</td>
</tr>
</tbody>
</table>

Morphologic and immunohistochemical evaluation of splenic hematopoietic proliferations in neoplastic and benign disorders

Distinction between subtypes of AML is difficult and rarely required

Myeloid Neoplasms and Extramedullary hematopoiesis

- All cause diffuse splenic enlargement
- All show red pulp involvement
- Distinction between subtypes of AML is difficult and rarely required
Essential Thrombocythemia
- Very little splenomegaly
- Large masses of platelets in red pulp
- Multiple infarcts in advanced cases
- No neoplastic myeloid proliferation (5-10% evolve to post-ETMM)

Polycythemia Vera
- Erythrocytotic phase
  - moderate splenomegaly
  - congestion of cords and sinuses only
  - Little neoplastic myeloid proliferation
- Spent phase (15% cases)
  - marked splenomegaly
  - indistinguishable from CIM

Splenic CIMF case #7
- 55 year-old man presented with weakness, fatigue and a big spleen
- PB showed a leukoerythroblastic anemia
- Spleen removed for cytopenias
- Gross: 4,200 gm. spleen; beefy red, homogeneous appearance
Nodular proliferation in CIMF “plum”
In this case, megakaryocytic plum

EVALUATION OF “MYELOID METAPLASIA” IN SPLEEN

**Reactive**
- Hematopoietic – hemolytic anemias, other anemias: predominantly erythroid with occasional megakaryocytes
- Cytokine-induced (e.g. G-CSF): predominantly myeloid – may simulate AML, M2 or M3 in particular
- Associated with lymphoma/ malignancies (carcinoma): variable degrees of lineage hematopoiesis

**Clonal**
- CIMF: trilineage – occasionally one lineage predominates
- CML: predominantly myeloid
- CMML: predominantly myeloid occasionally with increased monocytes/macrophages
- Other MDS/MPD: variable

**Chronic Myelogenous Leukemia**
- Diffuse enlargement (multinodular may be seen in blastic phase)
- Predominantly granulocytic infiltrate
- Ceroid containing macrophages (Gaucher-like)
CML: Immunohistochemistry similar to BMB

- **Stable phase:**
  - CD34-, CAE+, MPO+, lysozyme+

- **Blastic phase:**
  - CD34+, MPO+, TdT+, CD79a+, CD61/CD42b

**Differential Diagnosis: G-CSF effect**

- ET and PV (erythrocytotic):
  - Both: no myeloid metaplasia
  - Platelets stuffing of the RP cords and sinuses
  - Congestion of the RP cords and sinuses
  - Both proliferation of cordal macrophages

- CIMF/postpolycythemic myeloid metaplasia:
  - Large abnormal Megs.
  - Fibrosis and infarcts
  - Less numerous neutrophils, rarely left-shifted and blasts
  - Prominent intravascular erythropoiesis often megaloblastoid

- CML stable phase:
  - Small size Megs.
  - Less fibrosis
  - More numerous neutrophils, often left-shifted and blasts
  - Rare erythroblasts

**Chronic Myeloproliferative Disorders**

**Differential Diagnosis: G-CSF effect**

- anti-myeloperoxidase antibody

**AML in spleen (blastic transformation) case #8**

- 58 year-old woman with 8 yr. history of chronic myeloid leukemia in stable phase
- Recently increasing splenomegaly
- Pre-splenectomy bone marrow examination and PB findings consistent with stable phase CML (WBC 53x10⁹/L)
- Gross: 3,100 gr. spleen with an homogeneous red, 'beefy' appearance
AML: Histologic Features
- Diffuse: red pulp cords and sinuses
- Localized: myeloid sarcoma (chloroma)
- Intrasinusoidal only

Mastocytosis
- Case #6
- 74-year-old male with history of diarrhea, itching, headaches, bone pain, abdominal fullness
- Ultrasound examination showed enlarged spleen with abnormal signal
- Spleen 1,700 gr.

AML
- Precede, concurrent with systemic AML, or is manifestation of relapse
- Extramedullary blast transformation of MPD (most often CML)
- MDS/MPD (e.g. JMML, CMML)
- MDS (rare)

CD34+, AML

74 year-old male with history of diarrhea, itching, headaches, bone pain, abdominal fullness
Ultrasound examination showed enlarged spleen with abnormal signal
Spleen 1,700 gr.
### Non-Hematopoietic: Vascular Lesions

#### Vascular Lesions

- **BENIGN**
  - Hamartoma (more later)
  - Peliosis
  - Lymphangioma
  - Hemangioma
  - Littoral cell angioma

- **MALIGNANT**
  - Kaposi Sarcoma
  - Hemangioendothelioma
  - Angiosarcoma
  - Littoral cell angiosarcoma

#### Peliosis

- **Clinical:** Rare, unknown etiology
- **Gross:** Multiple cystic, blood-filled spaces. Spongy-appearing.
- **Micro:** Normal sinus lining, but dilated spaces. Cystic, blood-filled spaces.

#### Lymphangioma

- **Clinical:** Rare, benign disorder. Typically incidental finding. Multiple in lymphangiomatosis.
- **Gross:** Typically single, smooth-walled cyst, filled with clear fluid.
- **Micro:** Flattened, bland lining cells.
- **Immuno:** Variable FVIII/CD34/CD31+
- *NOTE: Lining is keratin negative, unlike mimic, mesothelial inclusion cyst*
Hemangioma, cavernous and capillary
- Clinical: usually incidental, unless part of congenital systemic form (hemangiomatosis)
- Gross: Red nodules, with irregular borders, spongy appearance
- Micro:
  - Cavernous: large caliber vessels, bland cytology
  - Capillary: small vessels, bland cytology. Variable degrees of sclerosis, often seen with a lobular architectural pattern
Littoral Cell Angioma

- Clinical: RELATIVELY COMMON
  - Often clinically silent, asymptomatic mass, discovered incidentally
  - Wide age range
  - Association with other malignancies; poorly understood

- Gross
  - Red pulp
  - Mass or multinodular; firm, bloody

- Microscopic
  - Anastomosing, patent vascular spaces
  - Lined by plump, splenic endothelial-derived cells
  - Occasionally papillary projections
  - Luminal macrophages
  - Mitoses rare
  - Macrophages may be prominent in cords
  - Variable fibrosis and sclerosis

Littoral Cell Angioma case #9

- 36 year-old female
- Pancreatitis with LUQ pain
- 10 cm splenic mass found on CT exam
- Poorly-circumscribed, bloody mass found in spleen
Non-Hematopoietic: Vascular Lesions

Littoral Cell Angioma

- Immuno
  - Positive for vascular markers
  - \textit{NEGATIVE} for CD34
  - Typically negative for CD8
  - Often positive for CD21

Kaposi Sarcoma

- Clinical: most typically seen in HIV/AIDS and other immuno-suppressed. Spleen is rare site of involvement usually part of disseminated disease
- Micro: Classic spindle shaped cells, slit-like vascular spaces, intracytoplasmic inclusions
- Immuno: CD31/CD34+, FVIII-, HHV-8+
Non-Hematopoietic: Vascular Lesions

**Angiosarcoma, littoral cell derived**
- (AKA littoral cell angiosarcoma)
- Microscopic
  - May have more widely patent lumens
  - May have more spindle-shaped cells
  - Immuno positive for CD8
  - Otherwise typical features including mitoses, necrosis, pleomorphism

![Angiosarcoma: 'typical'](Image)

![Epithelioid Angiosarcoma](Image)

![Spindled Angiosarcoma](Image)

![Littoral Cell Angiosarcoma](Image)
Non-Hematopoietic: IPT and Mimics

- Inflammatory Pseudotumor (IPT)
- Inflammatory Myofibroblastic Tumor (IMT)
- IPT-like Follicular Dendritic Cell Tumor (IPT-LFDCT)
- Capillary Hemangioma with Prominent Sclerosis

Inflammatory Pseudotumor

**Gross:** firm tan masses; variably well-circumscribed, not encapsulated

**Microscopic**
- Bland spindle cells
- Mixed inflammatory elements
- Prominent polyclonal plasmacytosis
- Lymphocytes, macrophages
- Varying sclerosis

Inflammatory Pseudotumor case #10

- 6 year-old female
- History of multiple UTI
- 1 cm splenic nodule found on CT scan
- Partial splenectomy
- 1 cm tan firm, well-circumscribed nodule
**Inflammatory Myofibroblastic Tumor**

**Gross:** firm tan masses; variably well-circumscribed, not encapsulated

**Microscopic**
- Spindle cell proliferation
- Varying inflammatory elements – typically fewer than IPT
- Composed of myofibroblasts
  - Actin and SMA positive
  - Cytogenetics may be positive for clonal disorder

**Non-Hematopoietic: IPT and Mimics**

**IPT-like Follicular Dendritic Cell Tumor**

**Gross:** firm tan masses; variably well-circumscribed, not encapsulated

**Microscopic**
- Proliferation of spindle cells
- Variable inflammation
- EBV-positive (EBER better than EBV-LMP)
- CD21/CD35 positive spindle cells
Non-Hematopoietic: IPT and Mimics

Capillary Hemangioma with Prominent Sclerosis
- Gross: circumscribed nodule, lobular pattern
- Microscopic
  - Lobular pattern
  - Sclerotic background with small arborizing vessels
  - CD34+, CD8- vascular spaces

SANT

Sclerosing angiomatoid nodular transformation ("acronymia")
Non-Hematopoietic: Cysts

- Pseudocyst (post-traumatic)
- Epidermoid
- Mesothelial inclusion cysts
  - (DDX: lymphangioma)

Non-Hematopoietic: Cysts

Pseudocyst (post-traumatic)
- Fluid-filled
- Variable size
- May develop as result of hematoma resolution
- NO EPITHELIAL LINING

Non-Hematopoietic: Cysts

Epidermoid Cyst
- As in other locations
- Has epithelial lining +/- additional structures
- May be filled with fluid or necrotic debris
Non-Hematopoietic: Hamartoma

- Classic Description
- Microscopic
  - Hemorrhage, infarction may be present
  - EMH may be present
- Immuno
  - CD8+ endothelial lining

Hamartoma: bland, red pulp histology
Hamartoma Subtypes

<table>
<thead>
<tr>
<th>Classical</th>
<th>Cord Capillary Hemangioma*</th>
<th>Myoid Angioendothelioma</th>
<th>Histiocyte-rich</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Obvious CD8+ sinuses</td>
<td>Predominant cord capillaries</td>
<td>Predominant myoid cells</td>
<td>Predominant histiocytes</td>
</tr>
<tr>
<td>Disorganized (cordal) stroma</td>
<td>Disorganized stroma, fibrosis</td>
<td>Cord capillaries</td>
<td>Cord capillaries</td>
</tr>
</tbody>
</table>

*May be the same as capillary hemangioma with sclerosis/SANT

Adapted from: Krishnan, Frizzera. Semin Diag Pathol, 2003;20(2).

Non-Hematopoietic: Metastases

- Splenic involvement with carcinoma is rare
- Local extension
  - Pancreatic
  - Gastric
  - Adrenal
- True metastases
  - Lung, breast, ovary
  - Choriocarcinoma
  - Other

Squamous cell carcinoma
Choriocarcinoma
Melanoma

Hamartoma Subtypes

Histiocyte-rich hamartoma

Semen Diag Pathol, 2003;20(2).