Non-neoplastic splenic disorders

**Splenic infarct**
Necrosis of splenic tissue due to occlusion of artery, usually presented in a wedge shaped area underneath the capsule
- Clinically presented with abdominal pain or asymptomatic
- Most commonly seen in hemoglobinopathy, autoimmune hemolytic anemia
- **Morphology:** Areas of necrosis have sharp demarcation from neighboring viable tissue, can be any size or morphology, but commonly in wedge shape underneath the capsule representing the area supplied by the occluded vessel
- Coagulative necrosis

**Red pulp congestion (hypersplenism)**
Expansion of red pulp with sequestration of red blood cells (most common), platelets, and/or granulocytes (less common)
- Most commonly seen in autoimmune hemolytic anemia, immune-mediated thrombocytopenic purpura (ITP), Felty syndrome, hereditary erythroid disorders (i.e. hereditary spherocytosis), erythrocyte enzyme deficiency (i.e. glucose-6-phosphate dehydrogenase deficiency, pyruvate kinase deficiency), hemoglobinopathy
- **Morphology:** Spleen is usually markedly enlarged. Sinusoids and cords in the red pulp are expanded, containing predominantly red blood cells. Platelets are increased in ITP. White pulp may be normal or hyperplastic
- **Differential:** Myeloproliferative neoplasms: Red pulp expansion with granulocytes, erythroid precursors, and atypical megakaryocytes

Benign splenic tumors

**Littoral cell angioma**
A benign splenic vascular neoplasm derived from splenic littoral cells (sinus lining cells)
- Occurs in both adults and children, median age of 49 years. No gender predilection
- **Clinical:** May present as hypersplenism and splenomegaly
- **Morphology:** Gross: multiple dark, spongy, cystic nodules, or solitary nodule in red pulp
  - Microscopic: variably sized spaces (slit, cystic) lined by single layer of littoral cells. The littoral cell morphology ranges from flattened to tall columnar with large vesicular nuclei, open chromatin, and small nucleoli. Desquamate into the lumen common. Fibrosis common
- **Phenotype:** CD8-, CD34-, ERG+, WT1-
  - Coexpress both vascular and histiocytic markers: tall columnar cells: CD68+, CD163+; flat cells: CD31+, factor VIII+
- **Differential:** Hemangioma: Most common benign neoplasm of spleen. Capillary or cavernous (more common), proliferation of vascular spaces lined by plump endothelial cells. No fibrosis. CD31+, CD34+, ERG+, CD68-, CD8-
  - Hemangiopericytoma: Benign vascular lesion consisting of spindle-shaped, uniform tumor cells grouped around dilated vascular channels. CD34+/-, CD57+/-, CK-, NSE-, SMA-. EM: myogenic-type intermediate filaments in basement membrane
**Hemangioendothelioma:** Vascular lesion with borderline malignant potential, consisting of well-formed vascular channels, mild cytologic atypia, low mitosis, absence of necrosis. CD34+, Factor VIII+, CD8-

**Hamartoma:** Tumor-like lesion consisting of structurally disorganized red pulp elements with or without fibrosis. Microscopically resembles red pulp with slit-like vascular spaces lined by plump endothelial cells. Trabecular structures derived from white pulp lymphoid cuff are present, but normal white pulp is absent. CD34-, CD8+

**Lymphoid and myeloid neoplasms primarily involving splenic red pulp**

**Hairy cell leukemia (HCL)**
An indolent B-cell neoplasm primarily affects spleen and bone marrow
Accounts for 2% of all lymphoid leukemias
Affects middle-aged and elderly, median age 58 years
Clinically presented as pancytopenia, monocytopenia, and massive splenomegaly

**Spleen: Gross:** homogenous, dark red in cut surface, usually diffuse without nodularity

**Microscopic:** Prominent red pulp expansion with diffusely infiltrated leukemic cells in cords and sinuses. Histologically the cells have round, oval, or bean-shaped nuclei with delicate chromatin, inconspicuous nucleoli, abundant pale cytoplasm with no visible cell border

**Cytology:** Cytoplasmic projections (hairs) all around the cell

**Blood lake:** Various sized “pools” of blood containing blood cells and leukemic cells

**Bone marrow:** Diffuse or paratrabeucular infiltrate, associated with fibrosis

**Phenotype:** All B-cell antigens+, monoclonal surface IG light chain+, CD11c+, CD25+, CD103+, CD123+, annexin A1+, TRAP+, BRAF+

**Genetics:** All cases are BRAF V600E mutated

**Prognosis:** Treatment includes cladribine, pentostatin. Indolent course with good prognosis (Additional description in lesson 7)

**Hairy cell leukemia variant (HCLV)**
A B-cell neoplasm primarily affects spleen, bone marrow, and blood
Accounts for 0.4% of all lymphoid leukemias
Affects middle-aged to elderly, median age 71 years
Clinically presented as leukocytosis (in contrast to HCL), anemia, thrombocytopenia, splenomegaly

**Spleen: Gross:** homogenous, dark red in cut surface, usually diffuse without nodularity

**Microscopic:** Prominent red pulp expansion with diffusely infiltrated leukemic cells in cords and sinuses. Histologically the cells are more heterogeneous from case to case, ranging from small round nuclei to larger cells with a prominent nucleolus, to cells with highly irregular nuclear contour. Cytoplasmic features are also variable, from scant to increased

**Cytology:** Cytoplasmic projection (hairs) similar to HCL, but may be less prominent

**Bone marrow:** Sinusoidal infiltrate

**Phenotype:** All B-cell antigens+, monoclonal surface IG light chain+, CD11c+/-, CD25-, CD103+/-, CD123-, annexin A1-, TRAP-, BRAF-

**Genetics:** No BRAF V600E mutation (distinguished from HCL)

**Prognosis:** More aggressive than HCL. Response to chemotherapy (but not to classic HCL therapy). Median survival ~9 years

**Splenic diffuse red pulp small B-cell lymphoma**
A B-cell neoplasm primarily affects spleen, bone marrow, and blood
Very rare, ~10% lymphoma diagnosed by splenectomy
Affects middle-aged to elderly, median age 67 years
Clinically presented as low lymphocytosis, thrombocytopenia, neutropenia, splenomegaly, occasional erythematous and pruritic skin papules

**Spleen: Gross:** homogenous, dark red in cut surface, usually diffuse without nodularity
**Microscopic:** Prominent red pulp expansion with diffusely infiltrated leukemic cells in cords and sinuses. Effaced white pulp. Histologically the cells have small round nuclei, mature chromatin, inconspicuous nucleoli, and increased pink/red cytoplasm. Low mitosis

Cytology: Short, broad based cytoplasmic projection, unevenly distributed around surface
Bone marrow: Sinusoidal infiltrate

**Phenotype:** All B-cell antigens+, monoclonal surface IG light chain+, CD11c+/-, CD25-, CD103-/+, CD123-, annexin A1-, TRAP-, BRAF-

**Genetics:** No *BRAF* V600E mutation (distinguished from HCL)

**Prognosis:** Indolent, response to splenectomy

### Comparison of cytologic and phenotypic features of B-cell neoplasms involving splenic red pulp

<table>
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<tr>
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<th>Hairy cell leukemia</th>
<th>Hairy cell leukemia variant</th>
<th>Splenic diffuse red pulp small B</th>
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| **Cytology**         | - Uniform small mature nuclei  
|                      | - Long cytoplasmic projections | - “Hybrid” feature of prolymphocytes and hairy cells  
|                      |                                 | - Short stubby cytoplasmic projections, uneven around cell surface |
| **Specific Phenotype** | CD11c+, CD25+, CD103+, CD123+, annexin A1+, TRAP+, BRAF+ | CD11c+/-, CD25-, CD103+/-, CD123-, annexin A1-, TRAP-, BRAF- | CD11c+/-, CD25-, CD103-/+, CD123-, annexin A1-, TRAP-, BRAF-  |

**Hepatosplenic T-cell lymphoma**
An aggressive T-cell neoplasm primarily affects spleen and liver without lymphadenopathy
Affects young adults, median age 35 years, male>female
Clinically presented as hepatosplenicomegaly and systemic symptoms (fatigue, fever, weight loss, night sweat), pancytopenia, high LDH
Bone marrow involvement in nearly all cases, peripheral blood involvement usually minimal

**Spleen: Gross:** homogenous, dark red in cut surface, usually diffuse without nodularity

**Microscopic:** Prominent red pulp expansion with diffusely infiltrated leukemic cells in cords and sinuses. Effaced white pulp. Histologically the cells have monomorphic, medium-sized, round nuclei, loosely condensed chromatin, small inconspicuous nucleoli, and a rim of pale cytoplasm. Some degree of polymorphism may be present

Bone marrow: involved in nearly all cases, sinusoidal involvement with or without diffuse interstitial involvement

**Blood:** usually not involved

**Phenotype:** T-cell phenotype (CD2+, CD3+, CD5-, CD7+, CD4-, CD8-/+, CD56+/-, CD57-), 80% TCR gamma-delta, 20% TCR alpha-beta, TIA-1+, granzyme B-, perforin-

**Genetics:** 50% Isochromosome 7q, 30% *STAT3B* mutated, 10% *STAT3* mutated

**Prognosis:** Aggressive, median survival <2 years, stem cell transplant improves survival
Differential: **T-cell large granular lymphocytic leukemia**: Older age, LGL cells in blood, B symptoms uncommon, TCR alpha-beta type in most cases, CD8+, CD57+, granzyme B+, perforin+, indolent course
(Additional description in lesson 10)

**Myeloproliferative neoplasms**
A group of chronic myeloid neoplasms primarily involving blood, bone marrow, and spleen
Splenic involvement is invariably present in chronic myeloid leukemia (CML), primary myelofibrosis (PMF), polycythemia vera (PV), and in a lesser degree essential thrombocythemia (ET)
**Spleen: Gross**: homogenous, dark red in cut surface, usually diffuse without nodularity
**Microscopic**: Prominent red pulp expansion with diffusely infiltrated leukemic cells in cords and sinuses. In CML and PMF, granulocytes and precursors predominant, with frequent atypical megakaryocytes and fewer erythroid precursors. In PV, erythroid precursors may be numerous, as well as myeloid precursors and megakaryocytes. In ET, splenic involvement is usually minimal
**Cellular morphology**: Myeloid precursors, megakaryocytes, erythroid precursors similar to cell morphology in bone marrow
**Phenotype**: Immunohistochemistry is useful to characterize cellular components: Myeloid: CD33, MPO; Erythroid: Glycophorin A, E cadherin; Megakaryocytes: CD61; Blasts: CD34
**Prognosis**: Splenectomy is usually not indicated. Persistent or progressive splenomegaly during therapy indicates transformation
(Additional description in lesson 15)

**Lymphoid neoplasms primarily involving splenic white pulp**

**Splenic marginal zone lymphoma**
A B-cell neoplasm arising from marginal zone of the splenic white pulp
Clinically presented with splenomegaly, usually symptomatic with abdominal fullness and abdominal pain, anemia, weight loss
Bone marrow involvement in >50%. Regional lymph nodes are frequent involvement, but no systemic lymph nodes involvement
**Spleen: Gross**: Nodular in cut surface representing the expanded white pulps
**Microscopic**: Numerous enlarged follicles with variably expanded marginal zones. Germinal centers and mantle zones may be preserved or obliterated by expanded marginal zone. The nodules may coalesce in advanced cases
**Cellular morphology**: Small to medium-sized round nuclei, clump chromatin with occasional small nucleoli, increased pale cytoplasm (“monocytoid”). Transformed large cells are present in single forms. Low mitotic activity
Bone marrow: Sinusoidal and interstitial infiltrate
**Phenotype**: All pan B-cell antigens+, monoclonal surface IG light chain+, IgD+, CD5-, CD10-, CD103-
**Prognosis**: Indolent. Usually treated with single agent chemotherapy. Splenectomy is both therapeutic and diagnostic
**Differential**: All types of B-cell lymphoma can secondarily involve spleen (primary in rare cases): Diffuse large B-cell lymphoma, Hodgkin lymphoma, Follicular lymphoma, Mantle cell lymphoma, Chronic lymphocytic leukemia/small lymphocytic lymphoma, etc
(Additional description in lesson 6)