Hematopoietic system - Introduction

**Myeloid Tissue**
- Bone marrow
- Blood cells
- Mononuclear-phagocyte system

**Lymphoid Tissue**
- Lymph nodes
- Spleen
- Thymus
- Accessory lymphoid tissue
Clinical evaluation of the hematopoietic system

- Some components easily accessible:
  - CBC
  - Blood smears
  - Peripheral lymph node aspirates
- Other components require more invasive techniques:
  - Bone marrow aspirates
  - Core Biopsies: lymph nodes, spleen and bone marrow
  - Necropsy: useful for lymphoid organs, less so for marrow

¹ These are evaluated by clinical pathologists
Myeloid system: Bone marrow and blood cells

Hematopoiesis

- The production of blood cells (hemopoiesis)

Blood cells are made in the following sites:

- Embryo: yolk sac
- Fetus: liver* and spleen*
- Neonates: mostly bone marrow (long & flat bones)
- Adults: bone marrow in all regions of flat bones & extremities of long bones
- Elsewhere depending on need
  - Extramedullary hematopoiesis (EMH)

Erythrocytes, leukocytes and platelets
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Myeloid system: Bone marrow and blood cells

Bone marrow of cattle of various ages

With age:
• Fat replaces the bone marrow in the diaphysis
Myeloid system: Bone marrow and blood cells

- Erythroid and myeloid precursors
- Vascular sinusoids
- Trabecular bone
- Osteoblasts
- Endothelial cells
- Megakaryocytes
- Stromal cells
- Adipocytes
Basic concepts of hematopoiesis

- Hematopoietic tissue is highly prolific
- All blood cells are derived from a common pluripotential stem cell
- Pluripotential stem cells are capable of self renewal and further differentiation
- Pluripotent stem cell → committed cells → maturing cells → mature cells
  - Mature cells have a limited lifespan
- Production and turnover of blood cells are balanced in health
Basic concepts of hematopoiesis

- Located in multiple sites but responds as a single tissue
- Samples can be taken from any bone with red marrow:
  - Proximal femur, iliac crest, proximal humerus of dogs and cats
  - Sternum of horses
  - Proximal rib of cattle
- Aspirates and core biopsies

Basic concepts of hematopoiesis

- Indicated when abnormalities are identified on hematology:
  - Unexplained cytopenias
  - Maturation or morphological defects (atypical cells in circulation)
  - Suspected myeloproliferative diseases
  - Potential malignancies metastatic to marrow

### Bone marrow: Microscopic evaluation

<table>
<thead>
<tr>
<th>Bone marrow aspirate/smears:</th>
<th>Important for:</th>
</tr>
</thead>
</table>
| Interpreted by clinical pathologists | • Cellular morphology  
• Erythroid to myeloid ratio  
• Primary or metastatic neoplasia |

**Should be interpreted in conjunction with a CBC!**

<table>
<thead>
<tr>
<th>Bone marrow core biopsy:</th>
<th>Important for:</th>
</tr>
</thead>
</table>
| Interpreted by morphologic pathologists | • Ratio of fat to hematopoietic cells  
• Myelofibrosis  
• Primary or metastatic neoplasia |

**Courtesy of Dr. Noel Clancey**
# Pathology of the Bone Marrow and Blood Cells

## End result depends on the type of cell damaged

- Pluripotent stem cells = multiple cell lines affected
- Committed stem cells = one or more lines affected
- Differentiated cells = one cell type affected

## Alterations are reflected in the peripheral blood

- Decreases in cell lines = cytopenias, anemia
- Increases in cell lines = ‘cytoses and ‘philias

## Alterations are reflected in the bone marrow

- Increased or decreased cellularity
  - Changes in the proportion of hematopoietic tissue (red marrow) to adipose tissue (yellow marrow)
- Changes in the erythroid to myeloid ratio
Pathology of the Bone Marrow and Blood Cells

I. Hereditary Disorders
- Covered in clinical pathology

II. Degeneration/Necrosis

III. Inflammation
- Covered in pathology of the skeleton

IV. Adaptations of growth
- Aplasia/Hypoplasia, Hyperplasia, Atrophy

V. Neoplasia
- Myeloproliferative & Lymphoproliferative Disease
Bone marrow and blood cells: Degeneration and necrosis

Hematopoietic tissue is highly active → susceptible to insults

- Radiation
- Toxins/Drugs
  - Chemotherapeutics
  - Immunosuppressant drugs
- Viral agents
  - Feline and canine parvovirus
  - Feline Leukemia Virus
  - Feline Immunodeficiency Virus
  - Equine Infectious Anemia
- Immune-mediated destruction
  - Systemic Lupus Erythematous
- Idiopathic

Bone marrow degeneration: canine parvovirus infection
Bone marrow and blood cells: Degeneration and necrosis

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BM necrosis is reflected in peripheral blood as cytopenias!
Bone marrow and blood cells: Adaptations of growth

Bone Marrow Hypoplasia / Aplasia

Bone Marrow Hyperplasia

Bone Marrow Atrophy (??)
Bone marrow and blood cells: Adaptations of growth

Bone marrow hypoplasia/aplasia

- Decreased/absent proliferative activity
- One or multiple cell lines can be affected

- Bone marrow suppression
  - Estrogen (exogenous and endogenous)
  - Chronic disease
  - Chronic renal disease
- Lack of nutrients
  - Iron
  - Vitamin B12
  - Folate
- Endocrine dysfunction
  - Hypothyroidism
- Bone marrow degeneration
- Idiopathic

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Bone marrow and blood cells: Adaptations of growth

**Bone Marrow Hypoplasia**

**Gross:**
- Increased yellow marrow

**Normal bone marrow**

**Hypoplastic bone marrow**

**Histo:**
- ↑ ratio of fat to hematopoietic cells

~ 50/50
Bone Marrow Hyperplasia

- Proliferative response – May affect one/multiple cell lines
- Response to increased peripheral demand or hypofunction of blood cells:
  - Erythroid hyperplasia $\rightarrow$ response to anemia
  - Megakaryocytic hyperplasia $\rightarrow$ response to ↓ platelets
  - Myeloid hyperplasia (monocytic/granulocytic cell lines)
    - Neutrophilia $\rightarrow$ bacterial infections, tissue necrosis
    - Eosinophilia $\rightarrow$ parasites, hypersensitivities
    - Monocytosis $\rightarrow$ chronic infections, specific agents
Bone marrow and blood cells: Adaptations of growth

Bone Marrow Hyperplasia

Gross lesions:
- Red marrow replaces the yellow marrow
Bone Marrow Hyperplasia

**Histologic lesions:**
- Increased cellularity (↓ ratio of fat to hematopoietic cells)
- One or more cell lines can be affected
- Shift toward immaturity in the cell line
- Extramedullary hematopoiesis (spleen & liver) if severe
Bone marrow and blood cells: Adaptations of growth

What about bone marrow atrophy?

Serous atrophy of fat
Primary Hematopoietic Neoplasia

• Clonal proliferative disorders of hematopoietic cell types
• Affect primarily:
  • Bone marrow
  • The circulating blood (leukemia)
  • Lymphoid tissue (lymph nodes, spleen, thymus, etc)

• Common associated features:
  • Bone marrow hypercellularity
  • Anemia
  • Thrombocytopenia/neutropenia
  • +/- Leukemic cells in peripheral blood

• Divided into lymphoproliferative and myeloproliferative diseases:
  • Lymphoid cells: Lymphocytes (B and T Cells)
  • Myeloid cells: granulocytes (neutrophils, eosinophils, basophils), monocytes/macrophages, erythrocytes, and megakaryocytes
Primary Hematopoietic Neoplasia

- Hematopoietic Neoplasia
  - Lymphoproliferative Disease
    - Lymphoma
    - Lymphoid leukemia
    - Plasma cell tumours
  - Myeloproliferative Disease
    - Histiocytic Disorders
    - Myeloid leukemia
    - Myelodysplastic Syndrome
    - Mast cell tumour
Primary Hematopoietic Neoplasia

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Histiocytic Proliferative Disorders

1. Cutaneous histiocytoma
   - Common benign skin mass
   - Young dogs
   - Spontaneously regress

2. Reactive histiocytosis
   - Immunoregulatory disease
   - Waxing and waning, progressive
   - Cutaneous histiocytosis
   - Affects the skin
   - Systemic histiocytosis
   - Affects skin and viscera
3. Histiocytic Sarcoma

- Malignant neoplasia of dendritic cells or macrophages
- Breed predispositions
  - Bernese Mountain dog, Rottweiler, Flat-coated Retriever
- Can be solitary or multiple:
  - Solitary lesions
    - Surrounding joints, subcutis
    - Lymph nodes, spleen or liver
  - Multiple lesions
    - Disseminated histiocytic sarcoma (malignant histiocytosis)
3. Disseminated histiocytic sarcoma

- Aggressive multisystemic disease
  - Tumour masses in several organs: spleen*, bone marrow*, lymph nodes*, lung, skin
  - Splenomegaly, hepatomegaly
3. Disseminated histiocytic sarcoma

- **Histology**: Masses / diffuse infiltrates composed of atypical histiocytes
  - May be avidly hemophagocytic causing a non-regenerative anemia
Mast cell neoplasia

- Mast cells are widely distributed in the connective tissue, but they originate in bone marrow.

1. Cutaneous mast cell tumour
   - Common skin tumours of dogs

2. Alimentary mast cell tumour
   - Intestinal or gastric masses

3. Systemic mastocytosis
   - Involves primarily the hematopoietic system
3. Systemic mastocytosis = Visceral mast cell tumours

- Primarily involves the hematopoietic system
  - Spleen, bone marrow
- Rare: mostly cats

**Gross:**
- Diffuse splenomegaly
  +/- nodular surface

**Histology:**
- Cords and sheets of mast cells efface the parenchyma
Lymphoproliferative Diseases

- Hematopoietic Neoplasia
  - Lymphoproliferative Disease
    - Lymphoma
    - Lymphoid leukemia
    - Plasma cell tumours
      - Histiocytic Neoplasia
      - Myeloid leukemia
      - Myelodysplastic Syndrome
      - Mast cell tumour
  - Myeloproliferative Disease

Lymphoproliferative Disease

- Neoplastic disorders of lymphocytes
  - T cells and B cells (including plasma cells), Natural Killer (NK) cells
- Includes:
  - Plasma cell tumours
  - Lymphoid leukemia = Neoplastic lymphocytes in bone marrow and blood
  - Lymphoma = Neoplastic lymphocytes in tissues / organs
Plasma cell tumours

1. EM Cutaneous Plasmacytoma
   - Common skin masses in dogs
   - Surgical excision is usually curative

2. Extramedullary Plasmacytoma
   - Arising at sites other than BM / skin
   - Often affect the GI tract
   - Similar behaviour to skin lesions
   - Metastases rare
3. Multiple Myeloma

- Uncommon in domestic animals: dogs > cats
- Malignant tumour of plasma cell origin arising in the bone marrow
- Neoplastic (clonal) plasma cells secrete immunoglobulin leading to hypergammaglobulinemia:
  - Monoclonal gammopathy on serum electrophoresis
  - Hyperviscosity syndrome
  - Bence-Jones proteinuria
3. Multiple Myeloma

- **Gross:** Pale pink to dark red gelatinous masses replace bone marrow – typically multiple masses!
- **Histologically:** Sheets of round cells – with plasmacytoid morphology

Masses may occur in any bone, but most often occur in the vertebrae. Can see hypercalcemia due to ↑ osteoclastic activity *
3. Multiple Myeloma

- **Gross**: Pale pink to dark red gelatinous masses replace bone marrow – typically multiple masses!
- **Histologically**: Sheets of round cells– with plasmacytoid morphology
Clinical diagnosis of multiple myeloma is based on finding 2 - 3 + of the following features:

- Increased plasma cells in bm
- Punched out lesions on radiographs
- Monoclonal gammopathy
- Hypercalcemia
- Light chain (Bence-Jones) proteinuria

Affected bones often have “punched” out appearance on radiographs

Clinical signs: lameness, pain, lethargy, paraplegia

Slowly progressive