Pathology of the Hematopoietic System

Lecture 1: Introduction, Bone Marrow, and Blood Cells

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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\(^1\)
  - Blood smears\(^1\)
  - Peripheral lymph node aspirates\(^1\)

- Other components require more invasive techniques:
  - Bone marrow aspirates\(^1\)
  - Biopsies: lymph nodes, spleen and bone marrow (core)
  - Necropsy: useful for lymphoid organs, less so for marrow

\(^1\) These are evaluated by clinical pathologists
Blood cells are made in the following sites:

- Embryo: yolk sac*
- Fetus: liver, spleen, thymus, lymph node & bone marrow
- 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)

* Extramedullary hematopoiesis (EMH) - The process through which blood cells are made
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* Myeloid system: Bone marrow and blood cell development

**Hematopoiesis**

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Myeloid system: Bone marrow and blood cell development

Bone marrow of cattle of various ages:
- One day old
- 2 months
- One year
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 $\rightarrow$ committed cells $\rightarrow$ maturing cells $\rightarrow$ 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

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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 |

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

**Should be interpreted in conjunction with a CBC!**
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)
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
Hematopoietic tissue is highly active \(\rightarrow\) susceptible to insults

- Radiation
- Toxins/Drugs
  - Antineoplastic / immunosuppressive drugs
  - Idiosyncratic drug reactions
  - Toxic chemicals
- Viral agents
  - Feline and canine parvovirus
  - Feline Leukemia Virus
  - Feline Immunodeficiency Virus
  - Equine Infectious Anemia
- Immune-mediated destruction
  - Systemic Lupus Erythematosus
- Idiopathic

Bone marrow degeneration: canine parvovirus infection
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Reflected in peripheral blood as cytopenias!
Bone marrow and blood cells: Adaptations of growth

- Bone Marrow Hypoplasia / Aplasia
- Bone Marrow Hyperplasia

Serous atrophy of fat
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

Bone marrow and blood cells: Adaptations of growth
Bone marrow and blood cells: Adaptations of growth

Bone Marrow Hypoplasia

Normal bone marrow

Hypoplastic bone marrow

Gross → Increased yellow marrow

Histo → Increased ratio of fat to hematopoietic cells
• Proliferative response – May affect one/multiple cell lines

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

Bone Marrow Hyperplasia

Gross lesions:
• Red marrow replaces the yellow marrow
  • Metaphyses
  • Endosteal surface of diaphysis
  • Progresses to occupy entire marrow cavity
Bone marrow and blood cells: Adaptations of growth

Bone Marrow Hyperplasia

Myeloproliferative Disorders/Hematopoietic Neoplasia (esp leukemia) can look identical grossly.
Histologic lesions:

- Increased cellularity (decreased ratio of fat to hematopoietic cells)
- One or more cell lines can be affected
- Shift toward immaturity (e.g., left shift in neutrophils)
- Extramedullary hematopoiesis (spleen & liver) if severe
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
Lymphoproliferative Disease

- Neoplastic disorders of lymphocytes
  - T cells and B cells (including plasma cells), Natural Killer (NK) cells

- Includes:
  - Lymphoid leukemia = Neoplastic lymphocytes in bone marrow and blood
  - Lymphoma = Neoplastic lymphocytes in tissues / organs
Lymphoproliferative Disease: Lymphoma

*Lymphoma (lymphosarcoma) is one of the most common malignant tumours of domestic animals.

Affects many species

Etiology: Idiopathic (sporadic), Viral infections, Hereditary
Several methods of classification of lymphomas:

- **Anatomical classification**
  - Multicentric
  - Alimentary
  - Thymic
  - Cutaneous
  - Misc.
  - Leukemic

- **Cellular morphology**
  - Cell size
  - Nuclear features
  - Mitotic rate

- **Immunophenotype**
  - B-cell
  - T-cell
  - Non-B/T

- **Biologic behaviour**
  - Low grade (indolent)
  - Intermediate grade
  - High grade (aggressive)

- **Histologic pattern**
  - Diffuse vs follicular

- Newer classification systems use a combination of these methods
  - World Health Organization (WHO) system of classification of canine lymphoma
  - Also - clinical staging is important
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**Histologic pattern**
- Diffuse vs follicular

- B-cell lymphomas may have better survival profiles and response to treatment (compared to T-cell lymphoma)
- Small cell lymphoma with low mitotic rate → slow progression, poor response to chemotherapy
- Large cell lymphoma with high mitotic rate → rapid progression, but do respond to chemotherapy
Clinical Signs of Lymphoma

• Non specific signs:
  – Weight loss and loss of appetite
• Painless enlargement of lymph nodes
  – Lymphadenopathy
• Other signs depend on anatomic location:
  – Retrobulbar lymph nodes ➔ exophthalmos
  – Thymus ➔ dyspnea, esophageal obstruction
  – Alimentary ➔ diarrhea, obstruction or melena
Diagnosis of Lymphoma

- Fine needle aspirate of enlarged lymph nodes
  - Cytology
  - Immunocytochemistry
  - Flow cytometry
  - Clonality testing (PARR)
- Wedge/excisional biopsy of the lymph nodes
  - Histology
  - Immunohistochemistry
  - T cell vs B cell
- Necropsy
Moderately to markedly enlarged lymph nodes!

- Soft to firm, bulge on cut surface, homogenous, pale tan to white
- Foci of necrosis or hemorrhage are common
- Often firmly attached (fibrosis) to surrounding tissue
Organomegaly: diffuse organ enlargement

Multiple tan-white to pink nodules within organs

Thickening of walls of tubular organs

Gross lesions of Lymphoma
Neoplastic round cells efface the normal architecture

Low grade
Uniform population of small lymphocytes

High grade
Anaplastic round cells with mitoses, anisocytosis, anisokaryosis
Canine Lymphoma

- Most common canine hematopoietic neoplasia
- Usually middle aged to older animals
- 80-85% have multicentric lymphoma
  - Peripheral LN involvement is common
  - Usually medium to high grade
- Leukograms are usually normal

Multicentric Lymphoma

B cell lymphoma is most common
Canine Lymphoma

- No known cause (no viral association)
- Hypercalcemia of malignancy occasionally is seen in dogs with lymphoma → secretion of PTHrP

Lymphoma can also arise in the MALT and tonsils...
Feline Lymphoma

- Most common malignant neoplasm of cats
- Alimentary > multicentric > thymic > miscellaneous forms
- Peripheral LN involvement is uncommon
- Leukemia and bone marrow involvement are common
Association with Feline Leukemia Virus (FeLV):

- 10 -20 % of cats with lymphoma are FeLV +
- FeLV is associated with mediastinal and multicentric T cell lymphoma
- Young cats!
Questions?