Overview of Myeloproliferative Diseases, Terminology and Diagnostic Options

USEFUL DEFINTITIONS

Hematopoietic: Cells of either lymphoid (T lymphocytes, B lymphocytes and Natural killer lymphocytes) or myeloid origin (erythrocyte, monocyte, granulocyte, megakaryocyte) origin.

Leukemia: A neoplastic hematopoietic cell proliferation that has originated from the marrow (i.e. the process started in the marrow as opposed to in the tissues). Additional tests such as flow cytometry and the presence of certain markers is often needed to confirm where the neoplastic proliferation started. Once modifiers (such as lymphoid or myeloid) are added it helps indicate what cell type is involved.

Acute leukemia: Acute indicates that the neoplastic cells are immature and could be either of myeloid or lymphoid origin. In these cases, morphologic features may not allow conclusive identification of cell lineage (i.e. one cannot distinguish between myeloid or lymphoid origin based on visual inspection).

Chronic leukemia: Chronic designates a neoplastic proliferation of differentiated cell types (e.g. mature lymphocytes or mature myeloid cells). Of the chronic leukemias, chronic lymphoid leukemia is the most common.

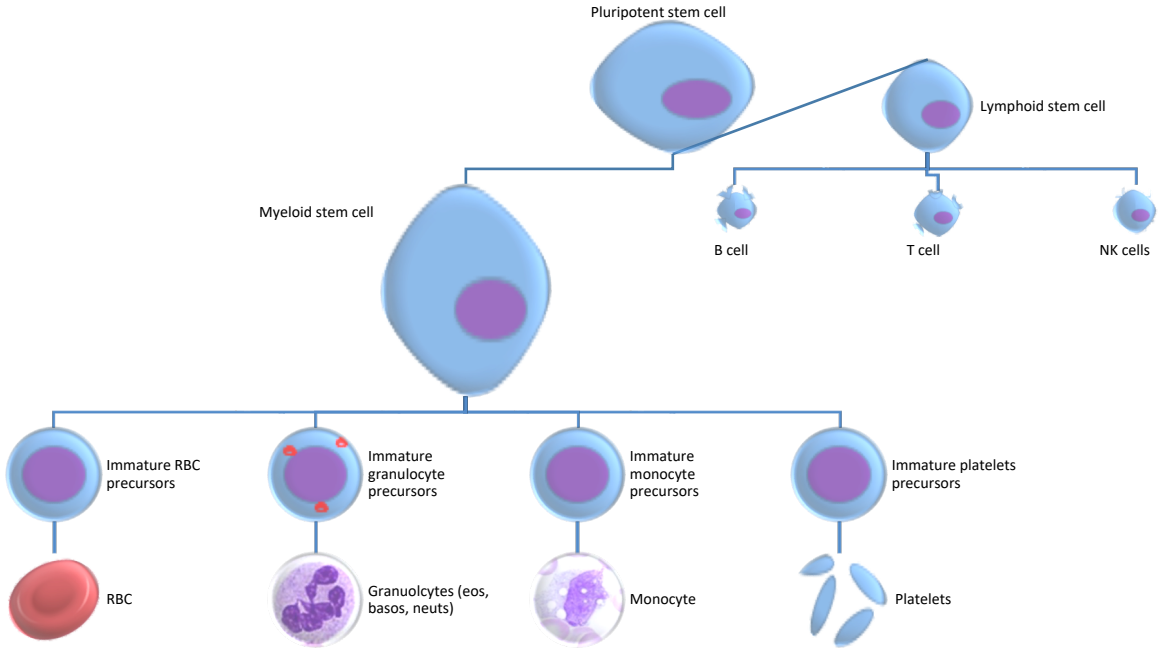
Leukemic: A term often used to indicate neoplastic cells in circulation regardless of their origin (e.g. bone marrow or tissue). However, this usage can often cause confusion.

Stage V lymphoma: Lymphoma, by definition, originates outside of the bone marrow. Neoplastic cells can enter circulation (stage V lymphoma) but this does not always indicate bone marrow infiltration. If the lymphoma is of a small origin, the cells in circulation will be small. If the lymphoma is of large cells, large cells will be found in circulation.

Myeloproliferative disease: Neoplasia with myeloid origins.

Myeloproliferative neoplasia (MPN): Neoplasia of myeloid origin of mature cells. Examples include polycythemia vera, chronic myeloid leukemia etc.

Reactive: Of a non-neoplastic origin.



INTRODUCTION TO MYELOPROLIFERATIVE DISEASES

Hematopoietic cells are derived from a pluripotent stem cell which gives rise to the lymphoid lineage and the myeloid lineage. Fully differentiated myeloid cells include RBC, granulocytes (comprised of neutrophils, eosinophils and basophils), monocytes and platelets. Each lineage is derived from an immature precursors (full maturation progression of all stages not shown).

Myeloproliferative diseases are divided into several groups. Neoplasms of immature myeloid cells are termed acute myeloid leukemia (AML). Disorders affecting mature myeloid cells are termed myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPN) (also known as chronic myeloid diseases). (Note that the term chronic myeloid leukemia is NOT an umbrella term for neoplasms of mature cells. Rather it is a specific entity designated by the BCR-ABL chromosome translocation).

MDS is a heterogeneous group of malignant hematopoietic stem cell disorders. It is characterized by dysplastic (atypical morphologic features) and ineffective blood cell production. There is a variable risk of transformation to acute leukemia.

MPNs are rare and are a diagnosis of exclusion; it is best to know the non-neoplastic (reactive) causes of increased numbers of mature myeloid cells (see below). MPN is not a diagnosis that can be made by doing a bone marrow; both reactive and neoplastic causes will have increased cells of that lineage in the marrow. The non-neoplastic causes (which are far more common than neoplastic causes) for increased mature myeloid cells are detailed below.

<u>ACUTE MYELOID NEOPLASMS</u>

1. Acute myeloid neoplasms are comprised of immature myeloid origin cells. Morphology can be insensitive marker of cell lineage. Meaning we may not be able to distinguish the origins (monocytic, granulocytic) of the cell line and we may not be able to distinguish it from immature lymphoid cells based on visual inspection. Note that PARR should not be used to distinguish lymphoid from myeloid cell origins as some myeloid cells can be PARR positive.

MYELODYSPLASTIC SYNDROME

1. MDS is a heterogeneous group of malignant hematopoietic stem cell disorders. It is characterized by dysplastic and ineffective blood cell production. There is a variable risk of transformation to acute leukemia.
2. Cats more commonly get MDS than dogs and it may be associated with FeLV positive status.
3. Can be primary → naturally occurring mutation in stem cell
4. Or secondary → acquired. E.g. mutation due to irradiation
5. Drugs or vitamin deficiency (cobalamin and folate) can mimic MDS
6. CBC findings
    a. In MDS, cells do not mature correctly, so lots of cells will be in the marrow but they don't make it out into circulation which results in cytopenias in the peripheral blood. You may also see atypical cells in circulation, most often represented by inappropriate metarubricytosis (in absence of regeneration) and/or macrocytosis in absence of regeneration
7. Marrow findings
    a. We use this term MDS if >10% of cells in the marrow show atypia. Atypia can be in one or more cell lines
    b. There should be <5% blasts (myeloblasts, monoblasts, promonocytes, erythroblasts, megakaryoblasts) in marrow
8. Classification
    a. There are many classifications for MDS but this is beyond the scope of the lecture
    b. In humans, MDS is classified using the World Health Organization (WHO) classification system based upon a combination of morphologic, immunophenotypic, genetic, and clinical features
    c. This classification attempts to identify biologic entities in hopes that future work will elucidate molecular pathways that might be amenable to targeted therapies

MYELOPROLIFERATIVE NEOPLASMS (MPN)

1. These diseases are *diagnoses of exclusion* characterized by excessive numbers of well-differentiated myeloid cells in circulation
2. In human medicine (and veterinary, to some degree), some have characteristic mutations which define them, however, we are not doing a lot of cytogenetics
3. NOTE bone marrow will not get you your answer. Both reactive and neoplastic causes will have hypercellular marrow smears. MPN will often have fibrosis in human literature
4. Chronic myelogenous leukemia
    a. Characterized by Philadelphia chromosome: BCR-ABL chromosomal translocations
    b. Analogous translocation in dogs, Raleigh chromosome, which is associated with CML in dogs
    c. Neutrophilia, basophilia, often eosinophilia +/- monocytosis, +/-thrombocytosis
5. Granulocytic forms
    a. Chronic neutrophilic leukemia, chronic eosinophilic leukemia
6. Polycythemia vera
    a. Often accompanied by neutrophilia, basophilia, thrombocytosis because a multipotent stem cell is mutated
7. Essential thrombocythemia
8. Primary myelofibrosis (aka Chronic idiopathic myelofibrosis)

a. Abundant fibroblasts secondary to cytokine release from a clonal, multi-lineage stem cell
b. Marked extramedullary hematopoiesis because of marrow changes
c. However, it should be noted that in people, the morphological phenotype of PMF can exist without the presence of overt bone marrow fibrosis (ie, prefibrotic PMF)

9. Monocytes
    a. Called chronic myelomonocytic leukemia (CMML)
    b. Not classifiable as MDS or MPN in humans
    c. Has peripheral monocytosis with dysplasia in the marrow
    d. Clinically: Cytopenias and hepatosplenomegaly

NON-NEOPLASTIC CAUSES OF INCREASED MATURE CELLS (WHICH CAN MIMIC MYELOPROLIFERATIVE NEOPLASMS)

CAUSES OF ERYTHROCYTOSIS

1. Relative: Dehydration, splenic contraction
2. Absolute:
    a. Secondary (stimulated by erythropoietin)
        i. Appropriate (e.g. as a result of hypoxemia)
        ii. Inappropriate (e.g. as a result of tumor producing erythropoietin)

CAUSES (MAJOR) OF LEUKEMOID RESPONSE (NEUTROPHIL NUMBERS {ANY AND ALL TYPES} >50,000/UL)

1. Immune-mediated hemolytic anemia (IMHA) with resulting tissue necrosis/death from severe anemia-induced hypoxemia (e.g. centrilobular hepatic necrosis) and/or thromboembolic disease
2. The 'Ps' – Pyometra (& stump pyometra), pyothorax, peritonitis (although this is infrequently a chronic condition), pyelonephritis (look for azotemia), pneumonia (chronic, not acute pneumonia), paraneoplastic (rare)
3. Neoplasia with necrotic portions of the tumor (outgrew its blood supply)
4. *Hepatozoon* infection (southern USA, Texas)

CAUSES (MAJOR) OF MONOCYTOSIS

1. Stress/cortisol-mediated
2. Chronic inflammation
    - With neutrophilia
3. Compensatory response (can occur with neutropenia)

CAUSES (MAJOR) OF EOSINOPHILIA

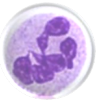
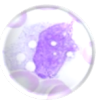
1. Worms, i.e. Parasites
2. Wheezes, i.e. Hypersensitivity reactions
3. Weird diseases (neoplasia, hypoadrenocorticism)

CAUSES (MAJOR) OF THROMBOCYTOSIS

1. Physiologic/redistribution
    - Epinephrine-mediated splenic contraction & release of platelet
    - Look for concurrent:

        - Mature neutrophilia (mild)
        - Mild lymphocytosis
        - ± Erythrocytosis

2. **Reactive (non-neoplastic) causes**
    - Chronic hemorrhage & Iron deficiency
        - (IL-6, +/- EPO)
    - Inflammation
        - IL-6 + other cytokines?
    - Decreased removal
        - Post-splenectomy
        - Steroids

Mature cell type		Non-neoplastic causes for increased numbers
 Red blood cells		Relative: hemoconcentration, redistribution, absolute: e.g. ↓FiO2, R→L shunt, Epo producing tumor
 Granulocytes	Neutrophils >50K	IMHA, pyometra, pyothorax, peritonitis, pyelonephritis, pneumonia, paraneoplastic, necrosis, Hepatozoon
	Eosinophils	Worms, wheezes, weird diseases
	Basophils	Usually similar to eosinophilia
Monocyte 		Stress/cortisol, chronic inflammation, compensatory
 Platelets		Reactive (chronic hemorrhage and iron def, chronic inflammation, decreased removal), splenic contraction

Myeloproliferative disease (myeloid neoplasms)	What we see in blood	Ancillary tests
Acute myeloid leukemia (AML)	Immature and/or poorly differentiated myeloid cells	Flow cytometry (preferred)
	can be difficult to tell which lineage is affected	PARR (May not distinguish myeloid from lymphoid)
	Immature myeloid cells can be difficult to distinguish from immature lymphoid cells based on morphology alone	Bone marrow (may not differentiate myeloid from lymphoid based on morphology alone)
Myeloproliferative neoplasms (MPN) (e.g. Chronic neutrophilic leukemia)	Excessive numbers of mature cell line (diagnosis of exclusion)	There are no markers for clonal proliferations of mature cell lines except Eos (therefore diagnosis of exclusion)
		Bone marrow NOT useful