Haemopoietic Neoplasia (Leukemia)

Leukemia is cancerous disorder of the blood-forming tissues (bone marrow, lymphatics, liver, spleen, thymus) , it is characterized by excessive production of immature or mature leukocytes and consequently a crowding-out of red blood cells and platelets.

Term definitions:

Leukemia: Literally means(white blood), it indicates neoplastic disorders that results from uncontrolled and excessive proliferation of haemoopoietic cells within the bone marrow leading to abnormal finding of large number of leukocytes in the peripheral blood. It may involve one cell line or a combination of cell lines.

Aleukemic leukemia: Occasionally, leukemic cells may not circulate in the blood and remain in the bone marrow.

Sub-leukemic leukemia: When low number of leukemic cells are rarely seen in the blood.

They may be divided into:

Myeloproliferative and lymphoproliferative neoplasia.

Myeloproliferative neoplasia(MPN):

It is a general term for all leukemias derived from myeloid cells normally produced in the bone marrow, other than the lymphocytes, it may involve one cell line or a combination of cell lines. Sarcomatous masses not tend to occur. Normal haemopoietic cells are displaced by the neoplastic population, resulting in myelophthisic disease. This kind of neoplasia is mostly observed in dogs and cats, it is rare in domestic and wild animals.

Based on the type of blood cell affected this type of neoplasia(MPN) may be divided into:

1. **Granulocytic leukemia (neutrophilic, basophilic and eosinophilic).**
2. **Erythremic myelosis(affecting RBC precursors only).**
3. **Erythroleukemia(affecting rbc and granulocyte precursors).**
4. **Monocytic leukemia, myelomonocytic leukemia (affecting granulocyte and monocyte precursors).**
5. **Megakaryocytic leukemia.**

Based on degree of differentiation and maturation of neoplastic blood cells, MPN may be divided into acute and chronic:

I- Acute Myelocytic leukemia(AML): Neoplastic cells are immature and they do not progress beyond the´ blast` stage (myeloid precursors). Neoplastic cells will undergo uninhibited proliferation of a clone of malignant myeloid cells leading to

increase in the number of immature myeloid cells (blasts) in the bone marrow and frequently in the peripheral blood. As blast cells accumulate in the bone marrow they replace the normal cellular constituents and results often in peripheral cytopenia (severe anaemia and thrombocytopenia). They are characterized by rapid onset and poor prognosis.

Clinical signs: Epistaxis, melena(black tarry faeces due to a partly digested blood from higher up the digestive tract) of acute onset, mucosal pallor with thrombocytopenic petechiation. Liver, spleen and lymph nodes are mostly normal or slightly enlarged. Death is mostly due to haemorrhage or septic infection.

Laboratory findings: Potential blood findings varies depending on subtype of leukemia, generally the following are to be expected:

a. Moderate or marked anaemia if accompanied with thrombocytopenic haemorrhage.

b. Blood film revealed presence of hypochromasia, plenty of Howell- Jolly bodies(due to splenic hyperactivity), mild anisocytosis poikilocytosis, reticulocytosis and rubricytosis. Thrombocytopenia, those present are with uniform basophilia and decrease in granulation and functional activity.

c. Total leukocyte count is highly variable(decrease, increase or normal) with myelocyte, promyelocyte, myeloblast dominating in a blood film.

Types of AML:

1- Acute undifferentiated leukemia: When blasts cells cannot be differentiated or identified with certainty.

2- Myeloblastic leukemia: It is also known as acute granulocytic or myelogenous leukemia, affected cell is the myeloblast, which may be neutrophilic, the most common type, eosinophilic or basophilic.

3-Promyelocytic leukemia: Myeloblasts and promyelocytes are the cells affected. It is characterized by great tendency for bleeding, it is a rare disease of young dogs that may die due to intracranial haemorrhage.

4- Acute myelomonocytic leukemia: Both myeloblasts and monoblasts are affected, it is a rare neoplastic disease of dog and cat.

5-Monoblastic leukemia: Affected cell is mainly monoblasts.

6- Acute monocytic leukemia: Promonocytes and to a lesser degree monoblasts are affected. Young dogs and cats\ are usually affected showing signs of recurrent epistaxis, vomting, anorexia and anaemia.

7- Erythroleukemia: Rubriblast and myeloblast are mostly affected with increase in erythroid and neutrophilic precursors, it is a rare disease in animals.

8- Erythremic myelosis: Precursors of rbcs are only affected, small to large number of nucleated rbcs are found in blood films without reticulocytosis or polychromasia that exclude responsive anaemia. It has been reported in cats, rare in other animals.

9- Megakaryoblastic leukemia: Megakaryoblasts are the cells affected.

2- Chronic myelocytic leukemia(CML):

Characterized by the excessive proliferation of neoplastic haemopoietic cells resulting in high number of mature well- differentiated cells in the blood, exhibiting a prolonged and progressive clinical course.

Clinical signs: History of gradual weight loss, extending over one- several months, anorexia, diarrhea, loss of condition, mucosal pallor, lymph nodes are normal or slightly enlarged, splenomegaly and hepatomegaly due to infiltration and proliferation of neoplastic cells in these two organs, clinical course is from 1-4 years.

Laboratory findings: CBC, reveals: mild to moderate non- responsive anaemia, plenty of Howell- Jolly bodies due to splenic overload, increase in wbc count(50-200/µl) with marked neutrophilic left shift. nuclei are mostly irregular and may be hypersegmented, mild increase in basophils, monocytes and eosinophils is occasionally observed, platelet number is normal or increased , then later in the clinical course it is decreased(variable).

Q: **How to differentiate between leukocytosis of CML and leukemoid reaction ?** In leukemoid reaction, there are toxic changes in the neutrophils, there is increase in inflammatory plasma protein in addition to clinical signs suggestive for inflammation.

however, there is a mixture of early mature neutrophil precursors, in contrast to the immature forms typically seen in acute leukemia.

Leukemoid reaction: It is characterized by a leukocytosis exceeding(25- 50,000 WBC/$mm^{3)}$ with a significant increase in early neutrophil precursors is referred to as a leukemoid reaction. The peripheral blood smear may show myelocytes, metamyelocytes, promyelocytes, and rarely myeloblasts;Leukemoid reactions are generally benign and are not dangerous in and of themselves, although they are often a response to a significant disease state.

However, leukemoid reactions can resemble more serious conditions such as chronic myelogenous leukemia (CML),

which can present with identical findings on peripheral blood smear.

Causes of leukemoid reaction:

1. Infection and inflammatory condition.
2. The use of certain drugs as sulfa and glucocorticosteroides.
3. Haemorrhage.

According to cell type affected CML is divided into:

1. Chronic myelogenous(granulocytic), reported in dogs and cats more than 5years old.
2. Chronic monocytic.
3. Chronic myelomonocytic.
4. Mast cell leukemia, very rare in dog and cat

Etiology: It has not yet been determined for the majority of species including dogs. Cats are an exception, as FeLV , FIV are frequently associated with MP disorders.

2.Lymphoproliferative neoplasia:

It includes any neoplastic expansion of lymphoid cells. It includes three broad categories:

1. Lymphocytic Leukemia: Lymphoid proliferation arising from transformation of lymphoid cells in the bone marrow.

2.Lymphoma: It is lymphoid proliferation arising outside marrow tissue.

3. Plasma cell neoplasm: It include neoplastic proliferation of plasma cells, it is considered separately from other lymphoid neoplasm including:

a. **Plasmacytoma:** The neoplastic cell arise outside the bone marrow.

b. **Myeloma:** Neoplasia arise from and involve the bone marrow

1.Lymphocytic leukemia: Neoplastic cell transformation can occur at any stage of lymphoid cell proliferation, according to stage of maturation of neoplastic cells, it may be divided into:

a. Acute lymphoblastic leukemia(ALL) and lymphoblastic lymphoma, it is due to neoplastic proliferation of poorly differentiated lymphoid cells.

2. chronic lymphocytic leukemia(CLL): It include neoplastic proliferation of more mature, differentiated lymphoid cells.

Q. Is there a difference between lymphoma and lymphosarcoma?

There is no difference between the two, the two terms indicate malignancy, there is no benign lymphoma all are malignant.

1.Acute lymphocytic leukemia (ALL, acute lymphoblastic leukemia, or acute lymphoid leukemia):

It is a proliferation of undifferentiated lymphocytes ,and considered the most common cancer in children. Even though the specific etiology is largely unknown, ALL is considered to be one of the most curable cancers in children. Although there are many similarities between the human and animal forms of the disease, the clinical course and outcome are very different. The prognosis with chemotherapy treatment is poor in canine and feline patients, and the average survival time is only a few months. Untreated, the estimated survival time from diagnosis is less than two weeks. ALL is more common in cats than in dogs, however neither is very common compared to lymphoma.

ALL begins with the malignant transformation of an undifferentiated lymphoblast in the bone marrow. The progeny of this single transformed cell are clones which proliferate rapidly. Varying numbers of these neoplastic cells can be found in the peripheral blood. As such, ALL is characterized by high numbers of lymphoblasts in the bone marrow and varying numbers of lymphoblasts in the blood. Leukemic profile stages include aleukemic (neoplastic blast cells in the bone marrow only – early stages), subleukemic (few blast cells in the blood) and leukemic (many blast cells in the blood). Therefore the peripheral white blood cell count (WBC) in these patients may be above, below, or within the reference range depending on the stage of the disease at diagnosis.

The cell of origin in ALL can be a B-cell, T-cell or NK-cell. Leukemias from all three cell types have been reported in dogs and cats Despite the origin, once a cell begins to proliferate the progeny typically do not mature and remain in the blast form in the marrow as well as in peripheral circulation. These cells do not function as normal lymphocytes. Instead, they compromise the normal function of the remaining hematopoietic precursors in the animal's bone marrow. This is called myelophthisis and may manifest as anemia, granulocytopenia, thrombocytopenia, or a combination thereof in the peripheral blood. The neoplastic lymphocytes can also involve the liver and spleen, as well as occasionally the lymph nodes, in the later stages of the disease.

Causes:

Although no exact cause for ALL has been isolated, some toxins and specific diseases have been indicated as predisposing factors. Human risk factors include specific

genetic diseases, as well as radiation exposure. FeLV has been implicated as a potential cause for ALL in cats. However, the correlation has become less common after the routine increase in FeLV testing and vaccination of cats.

Clinical Signs:

Most of the clinical signs associated with ALL are non-specific. Lethargy, anorexia, cachexia, vomiting, diarrhea, and persistent fever have all been commonly reported with the disease. On physical exam, splenomegaly, hepatomegaly, mild lymphadenopathy, pallor of the mucous membranes, and petechiae may be evident. Shifting leg lameness, epistaxis, dyspnea, tachycardia and recurrent infections have also been associated with ALL. Neurologic signs are less commonly reported.

Many clinical signs observed in ALL are the result of myelophthisis and the resulting cytopenias. Anemia leads to lethargy and pallor, thrombocytopenia leads to petechiae and epistaxis, and granulocytopenia leads to fever and infections. Other clinical signs are the result of tissue infiltration by leukemic cells and subsequent organ dysfunction.

Diagnosis:

Lymphoblasts are large lymphocytes (larger than a neutrophil) with a round nucleus and a scant to small amount of basophilic cytoplasm. They have a fine granular chromatin pattern and a visible nucleolus (Figure 1). ALL is often suspected after discovering moderate to high numbers of lymphoblasts in the blood (Figure 2).

Fig. 2

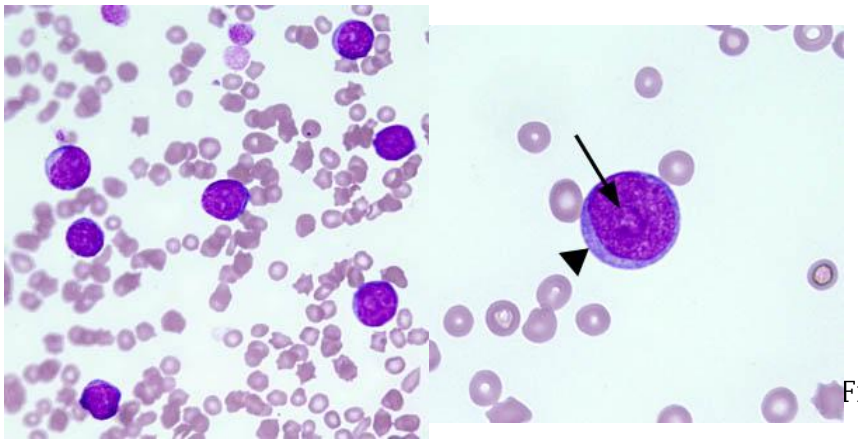
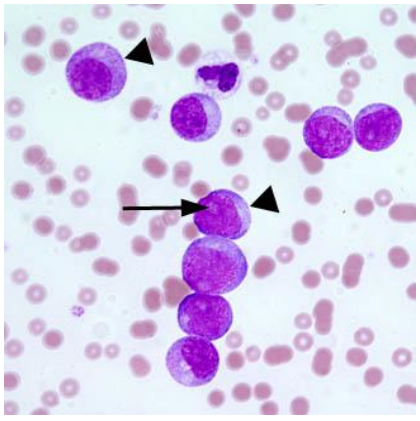


Fig.1

Figure 3. Acute myeloid leukemia in a cat. Numerous large myeloblasts with a moderate amount of lightly basophilic cytoplasm (arrowhead) and a visible nucleolus (arrow). Note the similarities to the lymphoblasts in Figures 1 and 2 that make it difficult to tell these cells apart based on visual clues alone

Fig.3



2.Chronic lymphocytic leukemia (CLL):

Other lymphoid neoplasm that must be differentiated from ALL as their prognosis, clinical course and treatments vary. CLL arises in the bone marrow like ALL but, unlike ALL, CLL is a malignant proliferation of lymphocytes with a mature or very well-differentiated appearance. These lymphocytes are small in size (smaller than a neutrophil) and their nucleus contains dense, clumped chromatin (Figure 4) and a very small amount of cytoplasm. CLL is suspected by finding high numbers of mature lymphocytes in the peripheral blood. Definitive diagnosis requires a bone marrow exam with greater than 30% small lymphocytes. Unlike ALL, CLL has a slowly progressive clinical course lasting months to years. Affected animals may be asymptomatic until late in the disease.

2.Lymphoma :

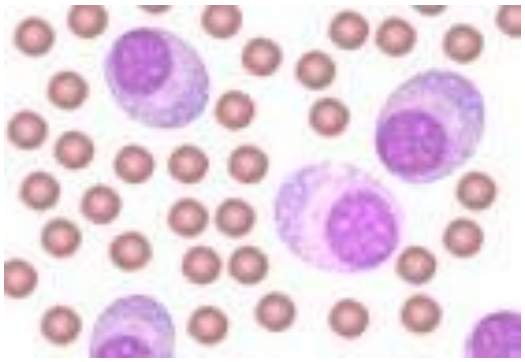
It is a malignant proliferation of lymphocytes, usually lymphoblasts, that originates outside the bone marrow. The most common sites of origin are lymph nodes but alimentary, splenic, thymic, mediastinal, renal and cutaneous lymphoma also occur. As lymphoma progresses, the neoplastic lymphocytes may infiltrate the bone marrow and blood making it difficult to determine the site of origin. When lymphoma involves the bone marrow or peripheral blood, it is referred to as stage V lymphoma. Several factors may be used to differentiate ALL from stage V lymphoma. First, ALL is not associated with solid tissue masses (lymphadenopathy, splenomegaly, hepatomegaly), whereas lymphoma is. However, if pancytopenia or systemic illness is present, ALL should be considered the most likely diagnosis.

Definitive diagnosis, however, requires bone marrow examination. Classically, greater than 30% of the nucleated bone marrow cells must be lymphoblasts to diagnose ALL. Fine needle aspirates of the liver and spleen can be helpful if these organs are enlarged and their involvement is suspected

3. Plasma cell neoplasm: We have to know what is a plasma cell A plasma cell is a mature B lymphocyte that is specialized for antibody (immunoglobulin) production. Plasma cells are rarely found in the peripheral blood. They comprise from 0.2% to 2.8% of the bone marrow white cell count.

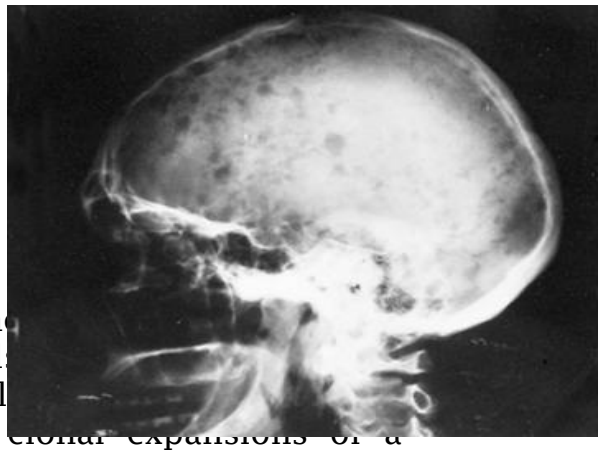
Mature plasma cells are often oval or fan shaped, measuring 8-15 µm. The nucleus is eccentric and oval in shape. The nucleus to cytoplasm ratio is typically 2:1 to 1:1. The nucleus may be

bilobed or multilobed, especially in patients with lymphoid blood dyscrasias. The perinuclear zone is very distinct, appearing white in the deeply basophilic cytoplasm. Nuclear chromatin is condensed and very patchy, appearing as dark blocks on a reddish-purple background. The cytoplasm stains deep blue to gray blue, depending on the stain and the ribosomal content of the individual cell. Plasma cells are seen in multiple myeloma, plasma cell leukemia. The cells depicted in this image are from a patient with plasma cell leukemia.



1.Multiple myeloma: It is an uncommon lymphoproliferative disease in animals, accounting for less than 8% of all hematopoietic tumors in dogs. No breed or sex predilections exist, and older dogs are most commonly affected, with a mean age of 8 to 9 years Multiple myeloma is even less common in cats, with a median age of 12 to 14 years and possible male predisposition.

Bony lesions in multiple myeloma. The skull demonstrates the typical "punched out" lesions characteristic of multiple myeloma. The lesion represents a purely osteolytic lesion with little or no osteoblastic activity.



Multiple myeloma is a B cell malignan
infiltration and growth of plasma cell
Normal B cells are transformed into mal
multistep process. Myeloma cells are clonal expansions of a neoplastic plasma cell, and they produce an identical, mostly immunoglobulin protein, called the *paraprotein* or *monoclonal (M) protein*, in large quantities. These paraproteins can often be identified as a monoclonal spike on a serum or urine protein electrophoretogram. The paraprotein may represent a complete immunoglobulin or a portion of the immunoglobulin (light or heavy chain)

Immunoglobulin G (IgG) and immunoglobulin A (IgA) gammopathies are the most common in people, dogs, and cats; immunoglobulin M (IgM) gammopathy (macroglobulinemia) is rare. Biclonal gammopathies, occasionally reported in veterinary patients, may be attributable to the development of two independent neoplastic clones, Pure light chain (kappa or lambda type) production, referred to as *light chain myeloma* or *Bence -Jones myeloma*, has rarely been reported in cats and dogs.

Pathologic effects:

The pathologic conditions associated with multiple myeloma are related to the effects of the circulating paraprotein as well as organ or bone marrow dysfunction due to neoplastic infiltration. High serum paraprotein(Bence-Jones protein) concentrations may result in hyperviscosity syndrome. Other conditions include osteolysis, hemorrhagic diathesis, cytopenias, hypercalcemia, renal disease, and increased susceptibility to bacterial infection.

CLINICAL SIGNS

Clinical signs associated with multiple myeloma, which are often nonspecific and insidious in onset, include lethargy, weakness, and anorexia. Polyuria and polydipsia can occur secondary to hypercalcemia or myeloma-related renal disease. Lameness, paresis or paralysis, and pain occur secondary to osteolysis or spinal cord compression. Bleeding diatheses, including epistaxis, gingival bleeding, intraocular hemorrhage, and, less frequently, melena or hematuria, are common. Retinal abnormalities occur frequently secondary to serum hyperviscosity and include retinal hemorrhage or venous dilatation with tortuous vessels. Central nervous system deficits, including dementia with midbrain or brainstem deficits, and seizures may also be present secondary to hyperviscosity syndrome or severe hypercalcemia. The median duration of clinical signs before presentation is 30 days in dogs

Diagnosis:

Diagnosing multiple myeloma is adapted from human medicine and requires confirming at least two of the criteria:

1. Detecting monoclonal gammopathy by applying electrophoresis to a serum or urine sample, it means observing the abnormal protein or immunoglobulin produced by the neoplastic plasma cell.
2 Detecting the abnormal protein(Bence-Jones) excreted with the urine.
3. Radiographic evidence for osteolytic bone lesions.

4. Detecting neoplastic plasma cells in the bone marrow(>10-20% neoplastic plasma cells).

2.PLASMACYTOMAS:

Clinical Presentation:

Extramedullary plasmacytomas are tumors of plasma cells that occur outside the bone marrow cavity. The most common location of these neoplasms is the skin or mucous membranes, especially the lip, digits, trunk, ears, and face.

Plasmacytomas are not very common tumors in dogs

Plasmacytomas are usually solitary raised nodules that appear red and sometimes ulcerated, especially neoplasm on the digits.

Cutaneous and mucocutaneous plasmacytomas usually lack clinical signs of disease; however, oral and rectal plasmacytomas have been associated with gagging or rectal prolapse, respectively.

Enzootic bovine leukosis (EBL)

EBL is characterized by the development of tumors of lymphatic tissues (lymphosarcoma), such as the thymus, spleen and lymph nodes. These specialized organs are an integral component of the defense system that protects the animal against infection by producing antibodies and specialized cells which attack bacteria or viruses.

Lymphoid cells are also found in other organ systems and circulating in the blood. Tumors may be found throughout the body; clinical signs of EBL depend upon their location. Enlargement of the external or superficial lymph nodes is common, but internal nodes may also be enlarged in the absence of external involvement.

Bovine leukosis, also known as bovine leukemia, is an infectious disease of cattle. It is caused by the bovine leukemia virus (BLV).

BLV is most commonly found in dairy cattle.

Infections have also been found in buffaloes and capybaras. Sheep can be infected; however the infection does not spread naturally to sheep.