LEUKOCYTES: DO NORMAL NUMBERS MEAN NORMAL PATIENTS?
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The leukogram, evaluated as part of the complete blood count (CBC), includes a quantification of the total number of white blood cells (WBCs) and the differential WBC count. Although a specific disorder is rarely diagnosed on the basis of a leukogram, the information obtained may be useful in limiting the number of differential diagnoses or in predicting the severity of the disease and its prognosis. Sequential leukograms may also be helpful in monitoring a patient’s response to therapy.

According to standard laboratory techniques, all nucleated cells are counted during a WBC count, including nucleated red blood cells (nRBCs). Differential leukograms determined by particle counters used at human referral laboratories are not valid for cats and dogs. New veterinary benchtop analyzers (LaserCyte and ProCyteDx, IDEXX, Westbrook, Maine) provide reliable WBC total and differential counts. The ProCyteDx provides a five-part differential WBC count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), and it includes flags for nRBCs and left shift/toxic changes. As a general rule, when a benchtop hematology analyzer yields values outside the reference interval or the values are flagged, the clinician or a technician should carefully examine the dot plot and a blood smear.

In some breeds of dogs (Belgian Tervuren, Greyhound) the WBC and neutrophil counts are frequently below the RI for the species, thus resulting in an erroneous diagnosis of leukopenia and neutropenia in an otherwise healthy dog. This should be kept in mind in dogs undergoing chemotherapy, since treatment delays based on a “low WBC or neutrophil” count (normal for the breeds) have a detrimental effect on the patient.

A differential WBC count may be reported in either relative (percentages) or absolute numbers (number of cells per microliter). However, the absolute leukocyte numbers, not the percentages, should always be evaluated because the latter may be misleading, particularly if the WBC count is very high or very low.

NEUTROPENIA

Neutropenia is relatively common in cats and dogs. The clinician should keep in mind, however, that normal cats may have neutrophil counts of 1800 to 2300/µL; this reference range is also true for Greyhounds and some of the other sighthounds.

In dogs and cats evaluated in a teaching hospital, infectious diseases (feline leukemia virus, feline immunodeficiency virus, parvovirus) are the most common comorbid conditions, accounting for almost 52% of the cases of neutropenia. Sepsis or endotoxemia accounted for 11% of the cases, as do drug-associated neutropenia (e.g., chemotherapy, phenobarbital, antibacterials); primary bone marrow disease is found in 4% of the patients. Border Collies commonly have neutropenia; this syndrome has been described as the “trapped neutrophil syndrome, an autosomal recessive trait due to a mutation in the VPS13B gene.
Clinical signs in neutropenic cats and dogs are usually vague and nonspecific; they include anorexia, lethargy, pyrexia, and mild gastrointestinal tract signs. Neutropenia is frequently an incidental finding in an otherwise healthy dog or cat (i.e., the patient is asymptomatic). If the neutropenia is caused by peripheral neutrophil consumption (i.e., a septic process), most animals exhibit clinical signs. Dogs and cats with parvoviral enteritis have neutropenia in association with severe vomiting or diarrhea or both. Cats and dogs with neutropenia can occasionally present in septic shock (pale, hypoperfused, hypothermic) and should be treated aggressively.

The evaluation of neutropenic cats and dogs should include a detailed drug history (e.g., estrogen or phenylbutazone in dogs, griseofulvin in cats); vaccination history (e.g., was the cat vaccinated against panleukopenia or the dog against parvoviral enteritis?); a complete physical examination and imaging in search of a septic focus; serologic, virologic, or molecular tests for infectious diseases (e.g., feline leukemia virus, feline immunodeficiency virus, canine ehrlichiosis and anaplasmosis, parvoviral enteritis); and, if necessary, bone marrow cytologic or histopathologic studies. Evaluation of changes in a blood smear is important in establishing the pathogenesis of the neutropenia. As a general rule, benchtop hematology analyzers provide total neutrophil counts and do not distinguish mature neutrophils from bands, reemphasizing the value of evaluating the blood smear. As discussed above, the ProCyteDx provides a “left shift flag”. If a dog or cat has anemia and/or thrombocytopenia in association with the neutropenia, and if the anemia is nonregenerative, a primary bone marrow disorder should be strongly suspected. If a dog or cat has regenerative anemia and spherocytosis in association with neutropenia, an immune-mediated disease or hemophagocytic malignant histiocytosis should be considered in the differential diagnoses.

The presence of toxic changes in the neutrophils or a left shift (see below) tend to suggest infection (i.e., toxic changes and left shifts are typically absent in dogs and cats with steroid-responsive neutropenia or primary bone marrow disorders). Please remember that approximately 50% of the dogs and cats with severe inflammation have NORMAL total WBC and neutrophil counts! In a study of 248 dogs with toxic neutrophil changes conducted in Israel dogs with pyometra, parvoviral infection, peritonitis, pancreatitis, and septicemia were significantly, and not surprisingly, more likely to have toxic changes than those in the control group. Interestingly, toxic neutrophil changes were also significantly associated with acute renal failure, immune-mediated hemolytic anemia, and disseminated intravascular coagulation. Evaluation of sequential leukograms in neutropenic dogs and cats is helpful in excluding transient or cyclic neutropenia (or cyclic hematopoiesis).

As previously noted, normal cats and Greyhounds can have low neutrophil counts. Therefore if a cat or a Greyhound with a neutrophil count of 1800 to 2300/µL is brought in for evaluation (or, more likely, if the “neutropenia” is detected during a routine hematologic evaluation), a conservative approach (e.g., repeat the CBC in 2 to 3 weeks) is indicated as long as no other clinical or hematologic abnormalities are found (e.g., left shift, toxic changes).
Because corticosteroid-responsive neutropenia has been well characterized in cats and dogs, if most infectious and neoplastic causes of neutropenia have been ruled out in an asymptomatic neutropenic animal, an in-hospital therapeutic trial of immunosuppressive doses of corticosteroids (prednisone, 2 to 4 mg/kg/day PO for dogs; or dexamethasone, 4 mg/cat PO once a week) can be instituted. Responses are usually observed within 24 to 96 hours of the start of treatment in such patients. Treatment is continued as it is for dogs with immune hemolytic anemia and other immune-mediated disorders.

Asymptomatic, afebrile neutropenic dogs and cats should be treated with broad-spectrum bactericidal antibiotics because they are at high risk for sepsis. My drug of choice in dogs is sulfamethoxazole and trimethoprim, at a dosage of 15 mg/kg PO q12h; another drug that can be used in both dogs and cats is enrofloxacin (or other fluoroquinolones) at a dosage of 5-10 mg/kg PO q24h. Antibiotics with an anaerobic spectrum should not be used because they deplete intestinal anaerobes, a protective bacterial population.

Neutropenic febrile (or symptomatic) cats and dogs constitute a medical emergency and should be treated with aggressive intravenous antibiotic therapy. My treatment of choice consists of a combination of ampicillin (20 mg/kg IV q8h) and enrofloxacin (5-10 mg/kg IV q24h).

Neutrophil production can be stimulated by the administration of human recombinant granulocyte colony-stimulating factor (G-CSF) (5 µg/kg SQ q24h). Although results are quite spectacular, the responses are usually short-lived because of the counteractive effects of anti-CSF antibodies produced by the affected dog or cat. Lithium carbonate (10 mg/kg PO q12h) can increase the neutrophil counts in dogs; the therapeutic trough serum concentration of lithium is 0.8 to 1.5 mmol/L. Lithium carbonate does not appear to be effective in cats and may be toxic.

NEUTROPHILIA

The term mature neutrophilia refers to an increase in the number of segmented (mature) neutrophils without an increase in the number of immature forms (e.g., bands). Neutrophilia with a left shift refers to an increase in the number of both mature and immature neutrophils (more than 300/µL). A regenerative left shift is associated with increased numbers of immature neutrophils in which the number of immature forms does not exceed the number of mature neutrophils; most dogs and cats with a regenerative left shift have leukocytosis. A degenerative left shift occurs when the number of immature forms exceeds that of mature neutrophils; the number of the latter may be normal, low, or high. Degenerative left shifts are usually suggestive of an aggressive disease; toxic neutrophil changes (see previous section) are common in dogs and cats with degenerative left shifts. Disorders commonly associated with degenerative left shifts include pyothorax, septic peritonitis, bacterial pneumonia, pyometra, prostatitis, and acute pyelonephritis. The term extreme neutrophilia refers to situations in which the neutrophil count is above 50,000/µL; it can be associated with a left shift or mature neutrophilia. Diseases typically associated with extreme leukocytosis include septic foci (e.g., pyometra), immune-mediated diseases, hepatozoonosis, mycobacteriosis, and chronic myelogenous leukemia. A leukemoid reaction refers to a marked neutrophilia with a severe left shift, which includes metamyelocytes and myelocytes. It indicates severe
inflammatory disease and may be difficult to distinguish from chronic granulocytic (myelogenous) leukemia.

Although a high percentage of cats and dogs with neutrophilia have underlying infectious disorders, **neutrophilia is not always synonymous with infection**. Rather, neutrophilia in cats and dogs is commonly the result of inflammatory or neoplastic processes.

The endogenous release or exogenous administration of corticosteroids results in stress- or corticosteroid-induced neutrophilia. Other hematologic changes typical of a stress leukogram include lymphopenia, eosinopenia, and monocytosis (the latter does not occur in cats). These abnormalities are commonly seen in sick dogs and cats. Dogs with hypoadrenocorticism and inflammatory/infectious diseases typically lack the neutrophilic response of normal dogs (i.e., they are sick but do not have a stress leukogram).

Clinical signs in cats and dogs with neutrophilia are usually secondary to the underlying disorder. Pyrexia may or may not be present. If the patient has persistent neutrophilia, if the neutrophils display toxic changes, or if a degenerative left shift is present, every effort should be made to identify a septic focus or an infectious agent promptly. The workup in such animals should include a thorough physical examination (e.g., abscess); thoracic and abdominal radiography (e.g., pneumonia, pleural or abdominal effusion); abdominal ultrasonography (e.g., peritonitis, pancreatic or hepatic abscess); and the collection of blood, urine, fluid, or tissue samples for cytology and bacterial and fungal cultures.

The treatment of dogs and cats with neutrophilia is aimed at the primary cause. **EOSINOPENIA**

Eosinopenia is defined as an absolute decrease in the number of circulating eosinophils. It is commonly seen as part of the stress leukogram or with exogenous corticosteroid administration and is usually of little clinical relevance.

**EOSINOPHILIA**

Eosinophilia is defined as an absolute increase in the circulating eosinophil numbers. It is relatively common in small animals and can have a variety of causes. Because eosinophilia is quite common in dogs and cats with endo- or ectoparasites, no animal should undergo a thorough evaluation for eosinophilia before parasitic causes have been ruled out. In cats, flea infestation usually results in marked increases in the eosinophil count (i.e., >15,000/µL). In dogs, eosinophilia is frequently seen in roundworm and hookworm infestations or with dirofilariasis or dipetalonemiasis. Three additional relatively common causes of eosinophilia in cats include eosinophilic granuloma complex, bronchial asthma, and eosinophilic gastroenteritis. A clinical entity resembling feline hypereosinophilic syndrome has been reported in Rottweilers; in addition, lesions compatible with oral eosinophilic granulomas have been reported in Siberian Huskies. Eosinophilia can also occur in dogs and cats with mast cell tumors, but it is rare. In cats, eosinophilia may occur in association with lymphoma (i.e.; tumor-associated eosinophilia). Treatment is usually aimed at the primary disorder.

**BASOPHILIA**
Basophilia is defined as an absolute increase in the basophil numbers and is commonly associated with eosinophilia. Because basophils are similar to tissue mast cells, their numbers increase in disorders characterized by excessive immunoglobulin E production and binding and in a variety of nonspecific inflammatory and parasitic disorders. Dirofilariasis is always high in the list if the patient lives in a heartworm area.

**MONOCYTOSIS**

Monocytosis refers to an absolute increase in monocyte numbers. It can occur in response to inflammatory, neoplastic, or degenerative stimuli. In some patients with acute leukemia, the WBC dot plots reveal a large monocyte "cloud" of abnormal configuration, even though the total monocyte numbers may be normal. Although monocytosis has traditionally been observed primarily in chronic inflammatory processes, it is also common in acute disorders. The monocytosis in dogs is typically more pronounced than that in cats; monocytosis is extremely rare in Greyhounds.

Monocytosis is part of a stress leukogram in dogs. It can result from a variety of bacterial, fungal, and protozoal diseases. In the Midwest, systemic fungal disorders (e.g., histoplasmosis and blastomycosis) are relatively common causes. Because monocytes are precursors of tissue macrophages, granulomatous and pyogranulomatous reactions commonly result in monocytosis. In addition, immune-mediated injury resulting in cell destruction (e.g., immune hemolysis, polyarthritis) and certain neoplasms (e.g., lymphomas) may cause monocytosis. Some neoplasms secrete CSFs for monocytes and can result in marked monocytosis (more than 5000/µL). Although rare, monocytic leukemia can occur. The nature of the clinical evaluation in patients with monocytosis is similar to that used with neutrophilia: it should concentrate on identifying infectious foci.

**LYMPHOPENIA**

Lymphopenia constitutes one of the most common hematologic abnormalities in hospitalized or sick dogs and cats, in which it is attributed to the effects of endogenous corticosteroids (stress leukogram). Lymphopenia is also commonly identified in dogs and cats with chronic loss of lymph, such as those with chylothorax or intestinal lymphangiectasia. Contrary to popular belief, lymphopenia does not appear to predispose to infection.

**LYMPHOCYTOSIS**

Lymphocytosis is common in several clinical situations, including fear (cats), vaccination (dogs and possibly cats), chronic ehrlichiosis (dogs), anaplasmosis (dogs and cats), Addison’s disease (hypoadrenocorticism; dogs), and chronic lymphocytic leukemia (CLL). The lymphocytes are morphologically normal in all these disorders, with the exception of vaccination reactions, in which reactive lymphocytes (larger cells with a dark blue cytoplasm) are commonly seen. High numbers of morphologically abnormal (i.e., blast) lymphoid cells are found in dogs and cats with acute lymphoblastic leukemia.

Recent vaccination should be ruled out in dogs with lymphocytosis and reactive lymphocytes in the blood smear. Most dogs with lymphocyte counts >10,000 cells/µL have either chronic ehrlichiosis, CLL, or
leishmaniasis; dogs with monocytic ehrlichiosis or anaplasmosis frequently have increased numbers of
large granule lymphocytes (LGL), larger lymphocytes with abundant cytoplasm, and large azurophilic
cytoplasmic granules. LGL lymphocytosis can also occur in dogs with CLL. Lymphocyte counts of more
than 20,000 cells/µL are extremely rare in dogs with ehrlichiosis (i.e., dogs with more than 20,000
lymphocytes/µL more likely have CLL). The clinical and hematologic features of monocytic ehrlichiosis
and CLL are quite similar (e.g., cytopenia, hyperproteinemia, hepatosplenomegaly, lymphadenopathy).
Serologic tests or polymerase chain reaction (PCR) testing for *Ehrlichia canis*, immunophenotyping of
peripheral blood lymphocytes, PCR for clonality, and bone marrow aspiration findings may be helpful in
differentiating these two disorders.