Anemia in Cats (Part II)

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Editor’s Note: This segment of the two-part series discusses hemolytic and complex anemias in the cat.

Hemolytic Anemias

Autoimmune Hemolytic Anemia. Spontaneously occurring autoimmune hemolytic anemia is much more rare in cats than in dogs. Some cases thought to be autoimmune hemolytic anemia are probably hemobartonellosis. Moderate to severe anemia with reticulocytosis and a positive Coombs’ test are indicative of autoimmune hemolytic anemia. The mean corpuscular volume (MCV) is high in many cases. Because autoimmune hemolytic anemia can be secondary to other infectious or neoplastic diseases, and can be a component of systemic immune mediated disease (i.e. systemic lupus erythematosis), thorough examination of the cat is recommended.

Drug-induced Immune Mediated Hemolytic Anemia. Coombs’ positive hemolytic anemia is a rare complication in hyperthyroid cats treated with propylthiouracil (PTU). Severe anemia and thrombocytopenia have been seen in less than 10% of cats treated with PTU. Most affected cats recover if the drug is stopped and they are treated with supportive and immunosuppressive therapy.

Neonatal Isoerythrolysis. Blood type A kittens born to type B queens can die of acute intravascular hemolytic anemia caused by anti-A alloantibodies ingested in colostrum. Sensitization of the queen by previous pregnancy or transfusion is not necessary for the disease to occur.

Heinz Body Hemolytic Anemia. Oxidant agents affect erythrocytes in several ways. The clinical manifestation of oxidant injury depends on the degree and nature of the changes. Oxidation of the iron of hemoglobin—normally in the ferrous state—to ferric iron produces methemoglobin, which is not capable of oxygen transport. Oxidation of exposed sulfhydryl groups on hemoglobin causes formation of disulfide bonds and distortion of the tertiary structure of the hemoglobin molecule. The result is precipitation of hemoglobin. Precipitated hemoglobin coalesces to form the intracellular inclusions called Heinz bodies. Extensive Heinz body formation and attachment of Heinz bodies to the membrane increase the rigidity of the erythrocytes and render them susceptible to fragmentation and entrapment in the spleen where they are phagocytized. Oxidation of membrane proteins can cross-link areas of the membrane, likewise decreasing erythrocyte deformability.
Erythrocytes contain several systems to protect their components from the oxidants (e.g. superoxide anion and hydrogen peroxide) produced during normal metabolism. An enzyme called NADH-methemoglobin reductase uses NADH produced by glycolysis to maintain hemoglobin iron in the ferrous state by reducing the small amount of methemoglobin produced normally. Glutathione peroxidase degrades hydrogen peroxide and in the process reduced glutathione (GSH) is oxidized to GSSG (oxidized glutathione). GSH is maintained by de novo synthesis and by reduction of GSSG in a reaction involving glutathione reductase and NADPH produced in the pentose phosphate pathway. Defects in the protective mechanisms or exposure to agents that overcome the protective systems can produce methemoglobinemia and/or hemolytic anemia. Because cat hemoglobin has more exposed serum hepatitis groups than the hemoglobin of other species, cats are especially susceptible to Heinz body formation.

Extravascular hemolysis is predominant in many cases of Heinz body hemolytic anemia, but intravascular hemolysis can occur if membrane damage is severe (dependent on both dose and agent). The degree of anemia varies from subclinically mild to very severe. Reticulocytosis and macrocytosis are usual if the anemia is severe. Depending on the agent producing the oxidant injury, methemoglobinemia can accompany the hemolytic anemia. Some oxidant agents produce methemoglobinemia as the predominant form of erythrocyte injury, with Heinz body formation and hemolytic anemia only a minor component of the disorder.

Clinical signs of high methemoglobin concentration are cyanosis, dyspnea, and weakness. Because of the decreased oxygen content, blood with high methemoglobin concentration appears dark and brown; normal color is not restored by exposing the blood to air.

Small, nonpathologic Heinz bodies can be found in blood of most cats whether nonanemic or anemic due to other reasons. These small Heinz bodies in nonanemic cats have been called erythrocyte refractile bodies because they appear as shiny red to purple inclusions when a drop of blood-new methylene blue mixture is examined with a microscope. The presence of nonpathologic Heinz bodies in cats can be attributed to the increased susceptibility of cat hemoglobin to oxidative denaturation compared to other species and the structure of the cat spleen which makes it inefficient at pitting out small inclusions from erythrocytes. Therefore, anemia in a cat should not be attributed to oxidant injury unless Heinz bodies are large and erythrocyte shape abnormalities are evident in the routinely stained smear. Additionally, a reticulocytosis should be present.
Compounds that cause Heinz body hemolytic anemia:

*Propylene glycol*, a preservative used in soft-moist pet foods, is capable of producing Heinz body hemolytic anemia when fed in amounts found in commercial foods. Higher doses produce a greater effect. The anemia is mild and essentially subclinical.

*Acetaminophen* and *phenacetin* produce severe and often fatal disease in cats. The syndrome is associated with both intravascular and extravascular hemolysis and methemoglobinemia. Signs include vomiting, icterus, anorexia, cyanosis, facial edema, hemoglobinuria, and sometimes convulsions.

N-acetylcysteine given via nasogastric tube at an initial dose of 140 mg/kg followed by 70 mg/kg administered orally every six hours for 36 hours is an effective treatment if administered within approximately 24 hours of ingestion of the drug. A dose as small as two 325 mg tablets of acetaminophen can cause severe illness in a cat. Methylene blue, which is sometimes used to treat toxic methemoglobinemia in other species, should not be given to cats because it enhances the Heinz body formation and increases the severity of the anemia.

*Phenazopyridine*, a urinary tract analgesic, is another drug that should not be administered to cats because it produces Heinz body hemolytic anemia, methemoglobinemia, and hepatic injury.

Reported cases in cats had both extravascular and intravascular hemolysis.

*DL-methionine*, which is administered to cats to prevent signs of feline urologic syndrome (FUS), can produce Heinz body hemolytic anemia and methemoglobinemia at doses greater than 0.5 g/kg/day. Severity of the changes is dose related. Unidentified metabolites of methionine are thought to be the toxic compounds.

*Benzocaine*, a topical anesthetic, can produce severe methemoglobinemia in cats in a dose-related manner. Heinz bodies are not produced. Cetacaine, a benzocaine-containing spray for anesthetizing the larynx prior to intubation, should not be used in cats. Toxic methemoglobinemia with signs of cyanosis, dyspnea and vomiting was reported in a cat within 20 minutes of application of an over-the-counter skin cream (Lanacane) to pruritic areas by the owner.

*Onions*, probably the most common cause of Heinz body hemolytic anemia in dogs, also can cause anemia in cats if ingested in sufficient quantity.

*Endogenous oxidants*, of unknown nature, are considered to be the cause of Heinz body hemolytic anemia in some cats that have no known exposure to exogenous agents. Diabetes mellitus, lymphoma, and hyperthyroidism are several diseases in which concurrent Heinz body hemolytic anemia, presumably due to endogenous oxidants, has been recognized.

Complex Anemias

Many cats with moderate to severe, apparently nonregenerative anemias have multiple contributing causes. For example, a cat with traumatic blood loss anemia may not have an increased reticulocyte count until post-trauma inflammation and/or infection are resolved. The severity of anemia in a cat with chronic renal disease can be exacerbated by hematuria or gastrointestinal bleeding. Therefore, appropriate diagnosis and management of anemic cats should be based on consideration of all possible factors.

Anemia Due to Bone Marrow Neoplasia

*Myelodysplastic syndromes* and *acute myelogenous leukemia* are the two major categories of hematopoietic neoplasia (or myeloproliferative disorders).
Feline leukemia induced neoplasia of hematopoietic cells is one of the most common causes of severe, nonregenerative anemia in cats. Most affected cats have multiple abnormalities in peripheral blood, including anemia, lack of reticulocytosis, macrocytosis (MCV usually >55 fl), neutropenia, and thrombocytopenia. Some cats have high numbers of circulating nucleated erythroid cells. Myeloblasts or monoblasts circulate in peripheral blood in about two-thirds of cats with acute myelogenous leukemia. Diagnosis of hematopoietic neoplasia requires aspiration and examination of bone marrow.

Myelodysplastic syndrome is diagnosed if the marrow has less than 30% myeloblasts or monoblasts and characteristic morphologic changes of abnormal maturation are present in at least two hematopoietic cell lines (erythroid, granulocyte/monocyte, and megakaryocyte). Acute myelogenous leukemia is diagnosed on the basis of finding a myeloblast/monoblast count of greater than 30% of the hematopoietic cells. Hematopoietic neoplasias are best viewed as successive stages in the growth of a clone of cells derived from a stem cell that has undergone neoplastic transformation. A progressive block in maturation leads to underproduction of mature blood cells and accumulation of the immature—or blast—cells. Most cats that have progressed to a stage of myelodysplasia die or are euthanized at the time of diagnosis because of severe anemia or infection, some progress to overt acute myelogenous leukemia, some remain in a fairly stable state for variable periods, and a very few have been reported to recover. Acute myelogenous leukemia is a consistently fatal disease, but some cats diagnosed at this stage have lived for several months if given supportive care. There is no known specific therapy to effectively treat hematopoietic neoplasias.

Acute lymphoblastic leukemia is a lymphoid neoplasm that arises in marrow and results in replacement of normal hematopoietic cells by lymphoblasts. It is far less common than acute myelogenous leukemia. Affected cats may be only mildly anemic, but most are neutropenic and/or thrombocytopenic at the time of diagnosis. Most cats with acute lymphoblastic leukemia are FeLV-positive. Diagnosis is based on finding a marrow full of blast cells that do not have morphologic features or cytochemical reactions of myeloblasts or monoblasts. At Cornell University we routinely apply special staining procedures to smears of marrow to differentiate lymphoid from myeloid leukemias. Differentiating lymphoblastic leukemia from myelogenous leukemia is important since lymphoblastic leukemia generally is more responsive to chemotherapy and some degree of remission can be achieved in many affected cats.

Lymphoma (e.g. lymphosarcoma) is a lymphoid neoplasm that arises in extramedullary tissue and may secondarily infiltrate marrow. Lymphoma arising in the mediastinum is particularly likely to invade marrow. Extensive infiltration of marrow by lymphoma cells compromises hematopoiesis leading to anemia, neutropenia, and thrombocytopenia.

Multiple myeloma is a clonal neoplasm of plasma cells that may be found as diffuse or multifocal infiltrates of plasma cells in marrow and other tissues, particularly spleen and liver. Diagnosis is based primarily on detection of a monoclonal gammopathy and demonstration of plasma cell infiltrates. Anemia is a frequent but inconsistent finding.

Selected References:
The Cat's Meow

One of our professional members suggested that it would be helpful to have a regular column which provides practical clinic tips. We decided to introduce the column with the beginning of the New Year. This issue presents practical ideas suggested by Dr. John Saidla, feline extension veterinarian of the Cornell Feline Health Center. However, for future issues we will be depending on you for tips and ideas for this column. Submissions to this column can be made by following the instructions in the boxed insert on this page.

Anesthesia of vicious cats or cats that are easily upset can be accomplished by using a glass or plastic aquarium. Cautiously open the cage door and push the aquarium over the cat, tip it upright and slide a sheet of plexiglass or 1/4 inch thick piece of plywood over the top. Gas anesthesia can then be administered through an opening in the top via the hoses. When the animal is asleep it can be safely removed and further anesthetized.

Separating medical waste can be made more efficient if each container has listed on the side or top which type of medical waste is acceptable in that particular container. Writing the contents on the containers with a large permanent marking pen helps ensure correct placement.

Write the date of arrival on both ends of each vaccine box with a permanent marking pen will help ensure that the oldest vaccine is used first and rotation of vaccine stock is constant.

Placing small tissue biopsies on a piece of tongue depressor before placing in formalin will help the laboratory find and orient the correct top and bottom of the sample. When using a biopsy punch, place the removed section on the tongue blade and allow it to stick to the wooden blade by drying. Especially useful for punch biopsies of the skin.

Send your practical tips and ideas on feline health management to:

Cornell Feline Health Center
The Cat's Meow
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618 VRT
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Subject Index 1981-1990

Anesthetics/Drugs:
- A Guide to Feline Anesthesia, Spring '84
- Cats and Pharmaceuticals, Summer '84
- Synopsis of Cardiac Drugs, Vol 1(2)
- Using Organophosphates to Control Fleas, Vol 1(3)
- Side Effects of Megestrol Acetate Therapy, Vol 2(2)
- Telazol: A New Injectable Anesthetic, Vol 2(3)
- The Effects of Xylazine on Cardiac Function, Vol 2(4)
- Isoflurane: A New Inhalant Anesthetic, Vol 2(4)
- Analgesics: The Relief from Pain, Vol 5(2)

New Computer Program for Veterinarians, Winter '85
- Toxoplasmosis: Interpretation of Serologic Results, Summer '85
- Heartworm Antigen Test, Vol 1(2)
- Biopsy Principles, Vol 3(1)
- Panther Study Provides New Insight into FeLV Tests, Vol 3(1)

Endocrinology:
- Management of Diabetes Mellitus in the Cat, Nov '81
- Feline Hyperthyroidism, June '82
- Update on Hyperthyroidism, Vol 1(1)
- Treatment for Hyperthyroidism, Vol 1(2)

Fluid Therapy:
- Basic Principles of Feline Blood Transfusions, Vol 1(4)

Gastroenterology
- The Impact of Fecal Impactions, Vol 2(1)

Hematology
- Anemia in Cats, Vol 5 (4) & Vol 6 (1)

Hepatic Diseases:
- Feline Hepatic Lipidosis, Vol4(3)

Hospital Management:
- Virucidal Disinfectants, Vol 1(3)
- Selecting the Right Suture Material, Vol 2(1)

Neurology:
- Central Nervous System Disease in the Cat, Aug '81
- Autonomic Polyganglionopathy, Spring '83
- Peripheral Vestibular Diseases, Fall '84

Nutrition
- Guidelines to Selecting Patients for Nutritional Support, Vol 5 (3)

Oncology:
- Phototherapy of Cancer, Winter '83
- A Case for Chemotherapy, Spring '85
- Mammary Tumors Are Third Most Common Cancer in Cats, Vol 1(4)

Bacterial Diseases:
- Campylobacter jejuni and Cryptosporidia: Two New Causes of Feline Diarrhea, Winter '83
- Cats and Tuberculosis, Summer '83
- Cat Scratch Disease, Fall '83
- Salmonella Implicated as Cause of Songbird Fever, Vol 3(3)

Behavior:
- Feline Behavioral Problems, May '81

Cardiology:
- New Cardiovascular Studies, June '82
- Feline Heartworm Disease, Summer '85
- Synopsis of Cardiac Drugs, Vol 1(2)

Client Relations:
- The Veterinarian's Role in Bereavement, Oct '82

Dermatology:
- Eosinophilic Granuloma, Vol 1(3)
- A Differential for Oral Ulcers in Cats, Vol 2(2)

Diagnostic Tests and Aids:
- ELISA for Detection of Feline Coronavirus Antibodies, Nov '81
- New Computer Program Aids in Diagnosis, Fall '83
- Diagnostic Ultrasonography, Winter '84
- Feline Diagnostic Services at Cornell, Summer '84
- Understanding Coronavirus Serology Titers, Fall '84

Oncology:
- Phototherapy of Cancer, Winter '83
- A Case for Chemotherapy, Spring '85
- Mammary Tumors Are Third Most Common Cancer in Cats, Vol 1(4)
Effect of Radiation and Chemotherapy on Wound Healing, Vol 4(2)

Ophthalmology:
Intraocular Inflammation in Cats, Winter '84
Complicated Ulcerative Keratitis, Vol 2(4)

Parasitology:
Feline Haemobartonellosis, Summer '83
Feline Heartworm Disease, Summer '85
Feline Blood Parasites, Vol 2(3)

Toxicology:
Ethylene Glycol Intoxication in the Cat, Oct '82
A Review of Anticoagulant Rodenticides, Vol 1(3)
Lead Poisoning in Cats, Vol 4(1,2)

Respiratory:
Eustachian Tube Polyps: A Cause of Chronic Respiratory Distress, Fall '83
Radiographic Evaluation of the Dyspneic Cat, Win'85
Feline Bronchial Diseases, Vol 5 (1)
Dyspnea in a Cat with Otitis, Vol 5 (3)

Urology:
Micturition Disorders in Cats with Sacrocaudal Vertebral Injuries, Nov '81
Part 1: Understanding FUS, Fall '85
Part II: Understanding FUS, Vol 1(1)
Chronic Renal Failure, Vol 3(2)
Ruptured Bladder and Peritoneal Dialysis in a Cat, Vol 3(4)

Vaccines:
Compendium of Feline Vaccines, Fall '83
Rabies Vaccination Recommended for Cats, Fall '83
Using the New FeLV Vaccine, Spring '85
Explanation of FeLV Vaccine Guidelines, Summer '85
Vaccines and Adjuvants, Vol 4(1)
Should Cats be Vaccinated for FeLV?, Vol 5 (3)

Viral Diseases:
Immunopathogenesis of FIP, Feb '81
Herpesvirus Induced Atherosclerosis, Feb '81
New Insights in Gastrointestinal Viruses, Feb '81
Transmission of FeLV, May '81

Diagnosis of Virus Infections in Cats, Aug '81
Geographical Distribution of FIP, Aug '81
Feline Chronic Polyarthritis, Spring '83
Catpox Virus Infection, Summer '83
Recommendations for Prevention and Treatment of Kitten Mortality Complex, Spring '83
Understanding Coronaviral Serology Titers, Fall '84
Is Feline Leukemia Transmissible to Man?, Fall '85
Feline Immunodeficiency Virus, Vol 3(3)
The Immune Response to FIP in Cats, Vol 3(4)

Zoonoses:
Cat Scratch Disease, Fall '83
Toxoplasmosis: Interpretation of Serologic Results, Summer '85

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Meetings

Update on Leukemia Virus Vaccines and FeLV/FIV Testing

The American Veterinary Medicine Association Council on Biologic and Therapeutic Agents, the Feline Health Center and Office of Continuing Education at Cornell University's College of Veterinary Medicine are sponsoring a colloquium to provide indepth discussion of vaccines, testing and management of feline leukemia and feline immunodeficiency viruses. The meeting will be held at the Holiday Inn-International Drive in Orlando, Florida on March 1-3, 1991. For more information, please call Linda Ritzier at (607) 253-3200.

Third Annual Feline Seminar

Make plans now to attend the Third Annual Feline Seminar at Cornell University on August 2-5, 1991. Watch for more details in the next issue of Feline Health Topics.