CHAPTER 1

Anemia

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Overview

Anemia refers to a reduction in the oxygen-carrying capacity in red blood cells (RBCs). The presence of anemia is an indication of an underlying disorder causing a reduction in RBCs, not a specific diagnosis. Anemia is identified on blood work as a reduction in RBC count, packed cell volume (PCV), hematocrit (HCT), and/or hemoglobin. The normal RBC count in cats is lower than in dogs, and the regenerative bone marrow response to an anemia is typically slower [1, 2].

There are numerous causes of anemia in cats, and the diagnostic plan should investigate the cause of the reduction in RBCs. Based on the clinical presentation and diagnostic tests, the duration of anemia can help determine the underlying cause. In acute, rapidly progressing anemias, the clinical presentation may be more severe than in chronic, slowly progressing anemias. Cats with an acute anemia may demonstrate severe clinical signs with a moderate anemia (PCV or HCT 15–20%), while cats with a chronic anemia may present with minimal clinical signs with a severe anemia (PCV or HCT ≤ 10%) [1, 2].

Clinical signs will vary based on the severity of anemia, with a mild anemia presenting with mild, nonspecific signs (i.e., lethargy, decreased activity) while a severe anemia presenting with life-threatening signs (i.e., obtunded, dyspnea). Markedly anemic cats may exhibit pica, often manifested as eating clay-type litter. Physical examination may reveal pale mucous membranes, increased ventilatory effort (especially with stress), a soft, systolic heart murmur, tachycardia, and weakness. The presence of lymphadenopathy and splenomegaly could indicate a systemic disorder (i.e., neoplasia, infectious, and immune-mediated) [1, 2]. There are many known diseases that cause anemia in cats, and common disorders are classified and listed in Table 1.1.

The initial diagnostic step is to determine if the anemia is regenerative or nonregenerative. Circulating reticulocytes (immature RBCs) should be counted whenever the PCV or HCT is <20% to determine if the bone marrow is effectively producing RBCs. Cats have two types of reticulocytes, aggregate and punctate. Both aggregate and punctate reticulocytes contain residual ribosomes from RBC production (erythropoiesis), but aggregate reticulocytes have numerous dark staining clumps, whereas punctate reticulocytes contain small clumps or specks of ribosomal material. Aggregate reticulocytes are the most reliable indicator of a regenerative response and should be used to classify an anemia as regenerative or nonregenerative. There are two causes of a regenerative anemia, hemorrhage (blood loss) and hemolysis (blood destruction), and one cause of a nonregenerative anemia (decreased erythrocyte production). Nonregenerative anemias are commonly associated with a primary bone marrow disorder, but there are several extramedullary disorders that can prevent an appropriate regeneration response [1, 2].

TABLE 1.1: Classification and Common Causes of Anemia in Cats

Regenerative	*Hemolysis* • *Cytauxzoon felis* • Erythrocyte parasites (*Mycoplasma haemofelis* and *Candidatus Mycoplasma haemominutum)* • Heinz body anemia • Immune-mediated destruction (drug-induced, idiopathic, paraneoplastic, toxicity) • Methemoglobinemia • Microangiopathic hemolysis (DIC) • Neonatal isoerythrolysis • Oxidative injury (zinc, methylene blue, acetaminophen, benzocaine, phenazopyridine, onions) *Blood Loss* • Coagulopathy • External loss (urinary tract, trauma, epistaxis) • Internal or poorly visualized loss (gastrointestinal, peritoneal, pleural) • Trauma or surgical loss
Nonregenerative	*Intramedullary* • Hematopoietic neoplasia with or without feline leukemia virus or feline immunodeficiency virus infection • Lymphoproliferative neoplasia • Myelodysplasia • Myeloproliferative neoplasia • Red blood cell aplasia *Extramedullary* • Chronic inflammatory disease (e.g., fungal disease, feline infectious peritonitis, etc.) • Chronic renal disease • Neoplasia • Poor nutrition or starvation

Diagnosis

Primary Diagnostics

- Complete Blood Count (CBC): A CBC should be the first diagnostic test to be performed if anemia is suspected. Diagnosis of anemia requires the identification of RBC count, PCV, HCT, or hemoglobin below reference intervals. Although the regenerative status cannot be determined based on the CBC alone, RBC parameters (i.e., mean corpuscular volume [MCV] and mean corpuscular hemoglobin concentration [MCHC]) may provide some indication of regenerative status. Polychromasia is a good indicator of regeneration, although in cats, it may not be abundantly present in milder anemias. The presence of increased reticulocytes is the optimal way to differentiate between regenerative and nonregenerative anemias. Heinz bodies can be seen with oxidative injuries, although up to 5% of Heinz bodies can be seen in normal cats. Low MCV suggests iron

The Feline Patient, Sixth Edition. Edited by Lisa Durso Keel and Lisa Restine Drylewicz.

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deficiency anemia, which implies chronic blood loss. High MCV can be seen with regeneration but can also be a marker of feline leukemia virus (FeLV) infection. If the underlying cause of the anemia is associated with hemorrhage, mild to marked thrombocytopenia may be present. Additionally, if the underlying cause of the anemia is associated with poor bone marrow function, erythrocytes, platelets, and leukocytes may be decreased.

- Reticulocyte Count: Using new methylene blue stain, a blood smear should be evaluated to count aggregate and punctate reticulocytes (Figure 1.1). The feline response is slower and more subtle than dogs'. After 5–6 days and with sufficient anemia to stimulate erythrocyte production, the percentage of aggregate reticulocytes should be 1–5%. Feline reticulocytes and erythrocytes have some peculiarities, and if blood smear interpretation is difficult, consultation with a veterinary clinical pathologist may be needed. The reticulocyte count should be corrected for the HCT:
  - Corrected reticulocyte count = (reticulocyte %) × (patient's HCT/37.5%*)
    (*37.5% = normal HCT)
- Blood Smear Evaluation: The blood smear should be evaluated for morphologic changes, reticulocytes, and other erythrocyte precursor cells (Figures 1.1–1.3 and Web Video 1.1), RBC parasites, Heinz bodies (Figure 1.2), and cytopenias (i.e., platelets and erythrocytes). Because of the small size of feline erythrocytes, spherocytosis (indicative of immune-mediated destruction) is not easily detectable on feline blood smears.
- Feline Retroviral Screen: Anemic cats should be evaluated with an antigen test for FeLV and an antibody test for feline immunodeficiency virus.

Secondary Diagnostics

- Serum Chemistry Profile: A serum chemistry profile is indicated to detect underlying diseases, especially in cases of nonregenerative anemia. Particular attention should be given to serum color (hemolysis or icterus), blood urea nitrogen, creatinine, alanine aminotransferase, alkaline phosphatase, total bilirubin, and total protein.
- Bone Marrow Examination: With unexplained nonregenerative anemia, bone marrow aspiration and cytology are indicated (Chapter 218). Bone marrow slides should be submitted to a veterinary clinical pathologist, along with a tube of EDTA-anticoagulated blood drawn at the time of marrow aspiration or a CBC result. In some cases, a core biopsy of the marrow may be indicated.

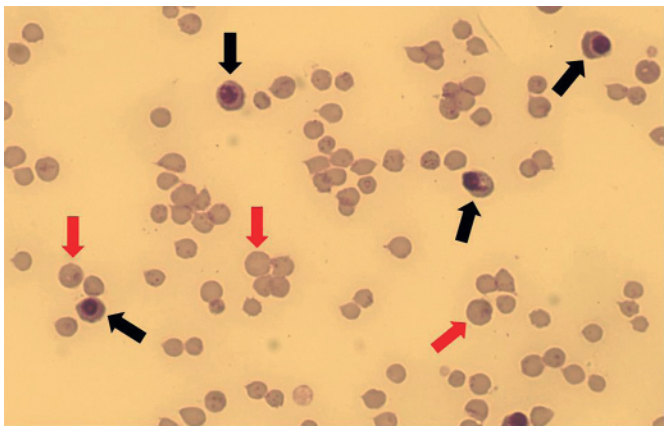

Figure 1.1 Signs of a regenerative anemia include the presence of nucleated RBCs and reticulocytes. Several metarubricytes (*black arrows*) and macrocytes (*red arrows*) are shown. Macrocytes are reticulocytes stained with a modified Wright's stain that demonstrate increased cell diameter but do not show the reticulum. The organisms on the RBCs are *Mycoplasma haemofelis*. Courtesy of Dr. Gary D. Norsworthy.

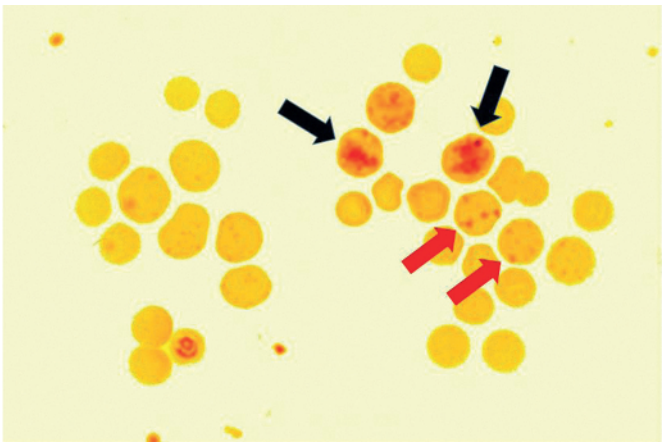

Figure 1.2 When stained with new methylene blue stain, reticulocytes demonstrate the reticulum as either younger aggregate reticulocytes (*black arrows*) or more mature punctuate reticulocytes (*red arrows*). Only aggregate reticulocytes are counted to generate the reticulocyte count. Courtesy of Dr. Gary D. Norsworthy.

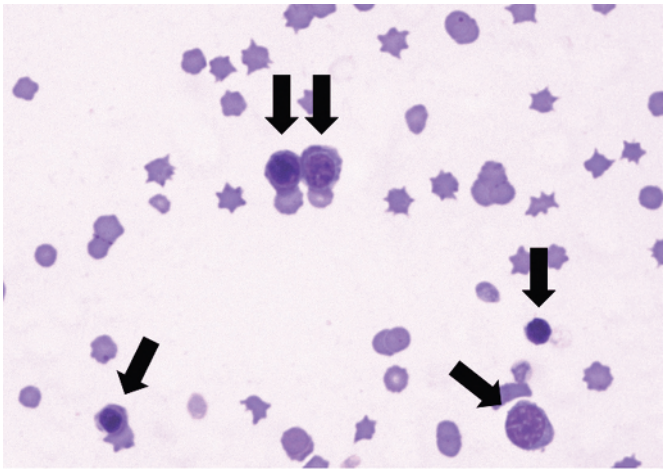

Figure 1.3 Although there are six nucleated RBCs in this image (*black arrows*), there are no macrocytes. Erythroleukemia results in an overproduction of immature RBC types, but they do not mature past the metarubricyte stage so the cat remains functionally anemic. Courtesy of Dr. Gary D. Norsworthy.

- Coombs' Test: A Coombs' test may be performed with a suspected immune-mediated cause of anemia. However, a positive Coombs' test result is not diagnostic for immune-mediated hemolytic anemia because a variety of disorders may produce a positive test result. An EDTA-anticoagulated tube of blood should be submitted to a veterinary diagnostic laboratory.
- Diagnostic Imaging: Radiographs (thoracic and abdominal) and ultrasound (primarily abdominal) may provide additional information about the underlying cause of anemia.
- Coagulation Tests: If coagulopathy is suspected, a manual platelet count and coagulation profile (prothrombin time and activated partial thromboplastin time) are indicated (Chapter 83).

Diagnostic Notes

- Mucous membrane color is a poor indicator of anemia in cats because normal feline mucous membranes are relatively pale, especially when compared to dogs, and mucous membrane color may increase with an increase in blood pressure due to excitement or stress.

- The presence of nucleated RBCs in circulation does not indicate a regenerative response unless there is a concurrent increase in aggregate reticulocytes. Causes of circulating nucleated RBCs in the absence of a regenerative anemia include neoplasia (Figure 1.1 and Web Video 1.1), hypoxic or toxic bone marrow injury, lead toxicity, and splenic disease.
- The bone marrow may require 5–6 days to produce an appropriate regenerative response following a significant anemia. This delay in regeneration should be considered if the initial hemogram and reticulocyte count are consistent with nonregenerative anemia, but hemorrhage or hemolysis is suspected.
- *Mycoplasma haemofelis* and *Candidatus Mycoplasma haemominutum* (Chapter 194) are bacteria that reside on the surface of the RBCs and are common causes of hemolysis in cats.
- Erythrocytes are at an increased risk of the development of oxidative injury because they carry oxygen, which can generate free radicals. To prevent oxidative injury, erythrocytes naturally contain several antioxidant mechanisms. However, when these antioxidant mechanisms are overwhelmed, free radicals can damage hemoglobin and reduce the oxygen-carrying capacity of the erythrocyte. Cats are more susceptible to oxidative injury because feline hemoglobin contains more sulfhydryl groups per molecule than that of other species and the spleen is inefficient at removing erythrocytes with oxidative damage [3].
- There are two main types of oxidative injury to feline erythrocytes: Heinz body formation and methemoglobinemia. Heinz body formation occurs when hemoglobin is denatured and precipitates on the RBC membrane. It is irreversible. Healthy cats can occasionally have Heinz bodies, but if excessive, the oxidative damage can cause hemolysis. Methemoglobinemia occurs when oxidative injury occurs to the ferrous iron in hemoglobin, reducing the oxygen-carrying capacity. Methemoglobinemia formation is reversible [3].
- Causes of Heinz bodies and methemoglobinemia include acetaminophen, benzocaine, copper, diabetes mellitus, DL-methionine, hyperthyroidism, lymphoma, methylene blue, naphthalene (moth balls), onions or onion powder, phenazopyridine, propofol, propylene glycol, vitamin K_3, and zinc [3].
- Heinz bodies can be identified using Wright's stain, but staining with new methylene blue allows for the easy identification of Heinz bodies [3].

Therapy

Primary Therapeutics

- Primary therapeutics should target the underlying cause of the anemia. If the primary cause is not treated, the anemia will persist or recur.
- Blood Transfusion (Chapter 217): Administration of whole blood or packed RBCs may be useful in cats with severe anemia; however, the decision to transfuse should be based on clinical findings and HCT. The use of the HCT alone is a poor indicator of the need for transfusion because cats with chronic severe anemia (PCV as low as 10%) may be stable and may not need a transfusion. Conversely, acute hemolysis or hemorrhage with a moderate anemia may warrant a transfusion, even if the HCT is 15–20%. Transfusion in cats with chronic anemia should be assessed on a case-by-case basis, although transfusion is usually needed when the HCT is <12%.

Secondary Therapeutics

- Erythropoietin: Feline recombinant erythropoietin is not commercially available. However, human recombinant erythropoietin may be used to help stimulate erythropoiesis in cases of anemia secondary to chronic renal failure. A human recombinant product, darbepoetin, is available and may have a lower risk of stimulating an immune reaction when compared to other erythropoietin products.
- Molidustat Oral Suspension: Varenzin™-CA1 (Elanco, Inc.) is a newly approved drug for cats with anemia due to chronic kidney disease. It induces the genetic transcription of erythropoietin, increasing both erythropoietin and RBC production in cats [4]. Further studies are needed to evaluate if this drug has uses in other causes of anemia.

Therapeutic Notes

- Emphasis should be placed on stabilizing the patient while aggressively pursuing the underlying disease process.
- Initial blood samples for diagnostic testing should be collected before blood transfusion.
- For cats with anemia of chronic disease, specific treatment for the anemia is rarely indicated, while identification and treatment of the underlying cause could lead to resolution.

Prognosis

Prognosis for a cat with anemia is dependent on the underlying cause and success of therapy. Early identification and successful management of the underlying cause of the anemia could lead to a positive prognosis. Generally, the prognosis is better for acute and regenerative than for chronic and nonregenerative anemias.

References

References for this chapter are found on the companion animal website at: www.wiley.com/go/dursokeel/6e.