

Approach to Anemia

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- anemia
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- bone marrow
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Anemia is a clinical sign, not a diagnosis. Defined as a decreased red cell mass, it results in insufficient oxygen delivery to the tissues. Anemias may be classified by red cell morphology into macrocytic, normocytic, and microcytic with increased, normal, or decreased mean cell volume (MCV), and normochromic or hypochromic with a normal or decreased mean corpuscular hemoglobin concentration (MCHC). Classification into regenerative or nonregenerative is helpful in understanding its pathophysiology and narrowing the list of causes. Regenerative anemia results when red cells are lost through hemorrhage or hemolysis. The marrow can expand its output up to 10 times the normal rate, so that low grade blood loss may be associated with reticulocytosis without anemia. It is only when the loss exceeds the rate of production that anemia results. Reticulocytes are released into the circulation in numbers that correlate with the rate of effective erythropoiesis in the marrow. The reticulocyte count represents the most important means for classification.

Acute blood loss results in loss of both red cells and plasma, so the major problem is hypovolemia; the hematocrit (Hct) remains normal. For this reason the Hct is not an accurate indicator of severity of ongoing bleeding. Twelve to 24 hours after blood loss, fluid shifts occur and the Hct drops. Reticulocyte counts do not increase significantly for 3 to 4 days after acute blood loss. Chronic blood loss results in depletion of red cells and nutrients, especially iron, with the circulatory volume remaining normal. Reticulocytosis gradually subsides, and a microcytic, hypochromic nonregenerative anemia results. Occult blood loss may occur due to blood-sucking parasites in pups or kittens or due to intestinal loss from parasites, tumors, or ulcers in adults. Internal hemorrhage may be more difficult to detect. Some red cells will be reabsorbed

from body cavities, and those that are damaged will give rise to a clinical picture more closely resembling hemolysis than hemorrhage. Causes of internal bleeding include trauma or tumors such as hemangiosarcomas. Coagulopathies can cause either internal or external blood loss. Platelet abnormalities cause petechiae or mucosal bleeding. Factor deficiencies are more likely to cause hematomas or bleeding into body cavities or joints.

Hemolytic anemia may be associated with icterus and other signs of systemic disease. Red cell destruction may occur in the circulation (intravascular hemolysis) and results in hemoglobinemia and hemoglobinuria. Hemolysis may also occur when red cells are phagocytized by the fixed macrophages in the spleen and other organs (extravascular hemolysis). Either type of hemolysis can cause icterus.

Nonregenerative anemia results from decreased production of red cells that usually have a normal appearance and life span. This may occur with primary marrow failure or when erythropoiesis is suppressed from an extramedullary cause. Retroviruses cause suppression of any or all hematopoietic cell lines and are the most common cause of severe anemia in cats.¹

Hormones, drugs, or chemicals such as cytotoxic antineoplastic drugs, chloramphenicol, endogenous or exogenous estrogen, benzene, and phenylbutazone are myelosuppressive.² Granulocytopenia and thrombocytopenia occur before anemia because red cells have the longest life span. Hypothyroidism may cause mild anemia. Rarely, macrocytic anemia occurs with decreased folate or vitamin B₁₂ levels in chronic intestinal disease. In renal failure anemia occurs because of decreased erythropoietin. A mild nonregenerative anemia may occur with any chronic, debilitating disease. Because of their normally short red cell life span, cats are more at risk than dogs. Anemia of chronic disease is associated with sequestration of adequate iron stores primarily in the marrow. The anemia is usually mild compared to the severity of signs of the underlying disease. The anemia resolves if the underlying disease improves. Immune-mediated destruction of red cell precursors may be a cause of red cell aplasia in dogs.³ The immune-mediated cause may be substantiated in some cases only in retrospect if a clinical response occurs with immunosuppressive drug therapy.

If the marrow fails to produce granulocytes and platelets as well as red cells, aplastic anemia results, with an increased risk of sepsis and bleeding. Known causes of peripheral pancytopenia and aplastic anemia include drugs (phenylbutazone, estrogen), infections

(ehrlichiosis, retroviral infections), immune-mediated causes, irradiation, neoplasia, myelofibrosis, or necrosis. A syndrome of idiopathic aplastic anemia has been recognized in six unrelated young dogs at Tufts Veterinary School.⁴ These dogs had severe pancytopenia, sometimes lasting several months; all recovered either spontaneously or with therapy. Treatment varied between cases but included transfusions as needed, immunosuppressive drugs (because of the possibility of an autoimmune cause), and, in one dog, hematopoietic growth factors. In myelophthitic anemia, neoplastic hematopoietic cells fill the marrow and inhibit normal hematopoiesis. These malignant cells may or may not appear in the blood, but neutropenia, anemia, and thrombocytopenia are usually present.

HISTORICAL FINDINGS AND THEIR MEANING

Observation of anemia in a young dog may be indicative of congenital disorders (e.g., pyruvate kinase deficiency in basenjis and beagles and phosphofructokinase deficiency in springer spaniels) or toxins (e.g., zinc ingested from eating pennies). Some breeds are predisposed to develop certain problems. Boxers are prone to neoplasia, German shepherds to hemangiosarcoma, and cocker spaniels to immune-mediated hemolytic anemia (IMHA). Old animals are more likely to have tumors, whereas middle-aged dogs are more likely to have immune-mediated anemia. Animals allowed outdoors may suffer from trauma, parasites, or infections (e.g., feline immunodeficiency virus [FIV]), or they may ingest toxins. Cats from multiple cat households are more likely to be exposed to feline leukemia virus (FeLV).

Any medication or recent vaccination should be considered as a possible cause of anemia. Drugs can be a cause of hemorrhage (nonsteroidal antiinflammatory drugs or aspirin), hemolysis (acetaminophen), or marrow suppression (phenylbutazone). Certain infections such as babesiosis, ehrlichiosis, or dirofilariasis are more likely in some geographic areas than others. Dietary deficiencies are uncommon with today's commercial diets. Young animals have low iron stores and become deficient more quickly than adults if iron is lost or missing from the diet. Additives such as onions or excessive copper can cause hemolysis.

PHYSICAL FINDINGS AND THEIR INTERPRETATION

Most anemic patients have pale mucous membranes, tachycardia, sharp pulses, and tachypnea. An assessment of the strength of the patient relative to the degree of anemia may provide subjective clues. A

slow onset of anemia as in marrow failure is associated with compensation so that the clinical signs may be minimal despite severe depletion of red cell mass. Icterus suggests acute hemolysis. A rough estimate is that the destruction of 4 g of hemoglobin (a drop of 12 percentage points in the Hct) in a 24 hour period may cause icterus even in the presence of normal liver function. Persisting icterus suggests hepatic or biliary disease.

Petechiae may be seen on the skin and mucous membranes and are most likely caused by thrombocytopenia. Accompanying anemia may be due to hemolysis or blood loss from mucosal hemorrhages throughout the gastrointestinal tract. If thrombocytopenia has been caused by marrow failure, anemia may be nonregenerative. Myeloma can cause bleeding from immunoglobulin coating of platelets and decreased production of red cells because of marrow invasion. Neoplasia or sepsis may cause anemia from disseminated intravascular coagulopathy with hemorrhage. Muffled heart sounds or abdominal distention may accompany bleeding into the pericardium, pleural cavity, or abdomen. These would be suggestive of factor deficiencies or a bleeding tumor such as a hemangiosarcoma. Gastrointestinal bleeding may be intermittent, and repeated testing may be necessary for detection.

Lymphadenopathy may indicate lymphoma with anemia resulting from myelophthisis, or may be secondary to FeLV, ehrlichiosis, or systemic granulomatous infections. Splenomegaly may occur but is not a specific sign. Oral ulcers or a uremic odor to the breath indicate renal failure. In dogs the signs of uremia are usually more severe than those associated with the anemia; in cats, however, anemia may be the primary sign of renal failure. Hyperestrogenism from a Sertoli cell tumor may cause marrow failure in dogs.

DIAGNOSTIC PLAN

A complete blood count (CBC) and reticulocyte count provide information as to the severity of anemia and initial classification. When blood is drawn, a drop should be placed on a slide and observed for autoagglutination. If it is present, a drop of saline is added to disperse rouleaux. If the agglutination remains, this is evidence of IMHA. Indicators of regenerative anemia are reticulocytosis, polychromasia, anisocytosis, and an elevated white blood cell count. Spherocytes may be seen in IMHA. Fragmented red cells may be seen in microangiopathic hemolysis. Acanthocytes (irregular projections from the red cell membrane) are seen with hemangiosarcomas and liver disease. Heinz bodies or brown blood (methemoglobin) are indicative of

oxidant toxins. Red cells should be examined for the presence of parasites. Nucleated red cells in the absence of reticulocytosis are *not* indicative of regenerative anemia.

Red cell indices either calculated or obtained from an automated counter are helpful. An increased MCV is usually associated with reticulocytosis. Some poodles have asymptomatic macrocytosis. In cats an increased MCV without reticulocytosis may be seen in FeLV infection and probably represents dysplastic maturation in the marrow. A decreased MCV is usually indicative of iron deficiency. Akitas and dogs with portosystemic shunts may also have decreased MCV. The MCHC may be decreased in the presence of reticulocytosis. The red cell distribution width represents one standard deviation from the MCV and provides specific information as to the variability of red cell size. For example the MCV could be normal if both macrocytic and microcytic red cells are present.

A direct antiglobulin (Coombs') test is positive in 60% to 70% of dogs with a clinical diagnosis of IMHA. In cats IMHA is often secondary to another problem. A test for FeLV and FIV should be run on every anemic cat regardless of the classification of the anemia. In both dogs and cats a minimum database should include a CBC, chemistry profile, urinalysis, and examination of the feces for color, consistency, and parasites.

If chronic blood loss is suspected, a fecal guaiac test for occult blood as well as measurement of serum iron is done. If fecal blood loss is substantiated and parasites are not found, a barium study or abdominal ultrasound examination may be performed to look for an intestinal lesion. Clotting tests are indicated if bleeding is present and a cause is not evident. In endemic areas dogs should be tested for microfilaria and for serologic evidence of ehrlichiosis. Thoracic and abdominal radiographs and ultrasound can be helpful in detection of malignancy.

Bone marrow examination is indicated if nonregenerative anemia, abnormal circulating cells, or monoclonal gammopathy are present. Such testing is not likely to add information if regenerative anemia is present. Hematopoietic malignancies tend to invade the marrow diffusely and are best detected by an aspirate. A marrow core biopsy is needed if the aspirate is hypocellular since the biopsy gives better information on cellularity or presence of myelofibrosis.

PROGNOSIS AND TREATMENT

In general, the prognosis is better in patients with regenerative anemia than in nonregenerative cases. Anemia from acute or chronic blood loss and hemolysis from parasites or toxins can usually be treated suc-

cessfully if the cause is removed. Immune-mediated thrombocytopenia (IMT) may be either transient or refractory. Postvaccinal IMT in young animals is associated with the best prognosis. Microangiopathic hemolysis is a sign of serious disease such as vascular tumor, splenic torsion, or disseminated intravascular coagulation (DIC).

IMHA may respond readily to immunosuppressive therapy, but relapses are common.³ The objective of treatment is to decrease the rate of removal of red cells and allow recovery of the Hct. Prednisone (2 mg/kg/day) is the first line treatment. Steroids inhibit binding of monocyte Fc receptors to IgG-sensitized cells and decrease erythrophagocytosis. The initial dose is continued until the Hct begins to rise, or for 2 to 3 weeks, and then decreased to 1 mg/kg/day for an additional 1 to 2 weeks. If the Hct continues to rise, treatment is reduced to a maintenance dose of 1 mg/kg every other day and is eventually tapered and discontinued while the Hct is monitored. If the Hct stabilizes in a safe range (usually over 20%), conservative treatment with the maintenance dose of prednisone can be continued for at least 1 to 2 months before addition of other medication, since the rate of rise in the Hct can be slow.

In cases where the Hct continues to fall despite steroids or in acute, life-threatening situations involving hemoglobinemia, hemoglobinuria, severe autoagglutination, or DIC, stronger immunosuppressive drugs are needed in addition to steroids. These include:

- Azathioprine^a—2 mg/kg/day for 1 to 2 weeks, then the same dose every other day
- Cyclophosphamide^b—2 mg/kg 4 days a week or every other day
- Cyclosporine^c—10 mg/kg/day IM daily for 5 days and then the same dose orally

These drugs may have to be continued for several months and slowly tapered with continued monitoring after treatment is stopped.

Danzol^d at 5 to 10 mg/kg twice daily has not been highly effective in dogs with acute severe hemolysis but may be of value when combined with steroids in some cases that are initially controlled with steroids but in which relapse occurs when the dose is decreased. Human γ -globulin^e at a single dose of 500 mg/kg IV has been beneficial in a few cases of refrac-

^aImuran®—Burroughs Wellcome.

^bCytoxan®—Bristol-Myers Squibb Oncology.

^cSandimmune®—Sandoz Pharmaceuticals.

^dDanocrine®—Sanofi Winthrop Pharmaceuticals.

^eGammar®, Immune Globulin USP—Armour Pharmaceutical Co.

tory IMHA. Splenectomy may be considered for dogs that relapse or require high doses of medication to control hemolysis. In addition, heparin is useful to prevent DIC and pulmonary thrombosis.

As reported by Switzer, the mortality rate in 77 cases of IMHA was 38%, with a slightly higher rate for males.⁵ Most deaths occurred within the first few days of illness and were associated with renal, hepatic, or cardiac failure or coagulopathy such as thrombocytopenia, DIC, or pulmonary thromboembolism. For those with fulminating disease the mortality is probably 75% to 80%.

Nonregenerative anemias from nutritional deficiencies, toxins, or treatable chronic diseases are most likely to respond, even in FeLV-positive cats. The prognosis is poor for most FeLV-positive cats with severe nonregenerative anemia. Human recombinant erythropoietin^f is effective in raising the Hct in pa-

^fEpogen®—Amgen.

tients with renal failure.⁶ Marrow failure from hyperestrogenism may be irreversible even if the cause is gone. Acute leukemias have a low remission rate since blast cells must be cleared from the marrow before normal cells return.⁷ A systematic approach to the anemic patient will allow for proper classification and result in accurate diagnosis, treatment, and prognosis.

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