Bella's Bad Blood

Canine Non-regenerative Anemia: A Review of Pure Red Cell Aplasia

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Introduction:

Bone marrow is not often thought about until something goes wrong with it. However, it is a vital organ responsible for production of erythrocytes, granulocytes, monocytes, and thrombocytes. An insult to the bone marrow, whether primary or secondary, can lead to major consequences. The focus of this paper will be on the abnormalities of erythrocyte production, with particular focus on non-regenerative anemia and pure red cell aplasia.

Pathophysiology:

Pure red cell aplasia (PRCA) is a hematologic condition in which the bone marrow is deficient of erythrocyte precursors. This process is likely immune-mediated, as evidenced by a response to immunosuppressive therapy and demonstration of antibody-mediated suppression of erythroid colony formation *in vitro* (8). PRCA is often considered to be a form of immune-mediated hemolytic anemia (IMHA) in which the immune-mediated destruction of erythrocytes occurs at the level of the bone marrow rather than in circulation. The result of this destruction is a non-regenerative anemia with erythroid hypoplasia or aplasia within the bone marrow (6). Non-regenerative IMHA is a similar condition in presentation but can be distinguished from PRCA by erythroid hyperplasia or erythroid maturation arrest in the bone marrow (6). PRCA has no known breed predispositions, and it most commonly occurs in middle aged dogs. A true sex predilection has not been determined, although, in a small retrospective study, females were overrepresented (7). Since this condition is uncommonly reported, most aspects of this disease are not well studied.

Presentation and Clinical Signs:

Most patients with anemia will present with non-specific signs such as lethargy, weakness, exercise intolerance, and anorexia (4). As with all patients, a thorough history and physical examination are important. A thorough history should include “vaccination status, diet, travel, life-style, duration of signs, drug or toxin exposure, prior or current illnesses, and similar illnesses in housemate or relatives” (1). On physical exam, there may be pale mucous membranes, tachycardia, and tachypnea due to decreased oxygen carrying capacity of the blood (4). With chronic anemias, which are generally non-regenerative, patients often present with only mild clinical signs despite a very low packed cell volume. On the other hand, acute anemias, in such cases as hemolysis and hemorrhage, are more likely to present with more severe clinical signs.

Diagnosis and Differential Diagnoses:

To diagnose anemia, a simple packed cell volume (PCV) is evaluated. Normal PCV in dogs ranges from 37% to 55%, and anemia is generally characterized as mild (30-36%), moderate (18-29%), or severe (<18%) (4). To diagnose the specific cause of anemia, it is easiest to start by further classifying the anemia as regenerative or non-regenerative. Regenerative anemia is broken down into the categories of hemolysis or hemorrhage. Hemolysis can be detected by the presence of icterus if extravascular hemolysis or hemoglobinemia/ hemoglobinuria if intravascular hemolysis. Specific tests such as a slide agglutination, blood smear, and Coombs’ test can be performed to further diagnose hemolysis. Hemorrhage can be obvious if petechia, bruising, hemoabdomen, hemothorax, hemopericardium, melena, or hematochezia is seen, but sometimes may be difficult to detect. Ultimately, to definitively diagnose anemia as regenerative or non-regenerative, a reticulocyte count is performed. The presence of reticulocytes (>1% or >80,000/µl) indicates that the bone marrow is actively

producing new red blood cells, while a low reticulocyte count (<1% or <80,000/µl) would point to a non-regenerative anemia (4).

Further characterization of the anemia using the mean corpuscular volume (MCV) and mean cell hemoglobin concentration (MCHC) can be helpful to differentiate some types of anemias. Most non-regenerative anemias, including PRCA, are normocytic normochromic (1). Macrocytosis can be indicative of regeneration, while iron deficiency can lead to microcytosis (1).

Once a non-regenerative anemia has been identified, the cause must be determined to be secondary or primary. Some secondary causes include acute blood loss or hemolysis in which the bone marrow has not had time to respond (first 3-5 days), anemia of chronic disease, decreased erythropoietin production due to chronic kidney disease, metabolic disease, infectious etiologies, drugs or toxins, nutritional deficiencies, or neoplasia (1). Some of the secondary causes can be easily ruled out. Chronic kidney disease can be eliminated by the absence of renal azotemia. Anemia of chronic disease is often only a mild anemia and is less likely if concurrent disease cannot be established (1). Drugs, toxins, and infectious agents can also be ruled out with a thorough history and proper diagnostic tests.

If a secondary cause of non-regenerative anemia cannot be determined, a bone marrow aspirate or biopsy is required to definitively diagnose a primary bone marrow disorder. When performing a bone marrow aspirate in dogs, appropriate sites for collection include the proximal femur, proximal humerus, iliac crest, and sternum (5). The most commonly preferred sites are the trochanteric fossa of the femur in small dogs and the iliac crest in large dogs (5). The risks associated with bone marrow biopsy are generally related to the sedation or anesthesia needed

and not the procedure itself. Hemorrhage and iatrogenic infection are possible but rare complications (2).

Evaluation of a bone marrow sample involves assessment of overall cellularity as well as individual cell morphology, size, concentration, and structure (2). The myeloid to erythroid ratio (M:E ratio) is calculated to measure cellularity of the marrow, with an increased M:E ratio a potential indication of erythroid hypoplasia. Selective erythroid hypoplasia or aplasia with a concurrent non-regenerative anemia is diagnostic of PRCA once all secondary causes have been ruled out (7).

Treatment:

A blood transfusion may be considered when a patient presents with clinical signs of anemia or if the PCV is below 15%. Since many patients with non-regenerative anemia usually require more than one transfusion, cross-matching and blood typing are important to remember to minimize to likelihood of a transfusion reaction.

Immunosuppressive therapy is the mainstay of treatment for immune-mediated anemias. Many options exist, including glucocorticoids, cyclosporine, azathioprine, cyclophosphamide, mycophenolate, and intravenous human immunoglobulin. Glucocorticoids, alone or in conjunction with another immunosuppressive, are the most common first-line treatment (3). The specific dosing, duration, tapering schedule, and drug choices vary among veterinarians and often depend on patient response as well as clinician preference. The side effects seen with glucocorticoid administration and the risks of immune suppression should be considered on a case-by-case basis. Many clinicians prefer to add another immunosuppressant to the treatment

regimen for patients taking glucocorticoids so that the glucocorticoid can be tapered more quickly to avoid long-term side effects, particularly in larger dogs.

Additional adjunctive therapies may be necessary such as additional transfusions, intravenous fluids, gastrointestinal medications, antibiotics, and/or anticoagulants. Although commonly performed in people with aplastic anemia, bone marrow transplants are not readily available to veterinary patients due to significant complications (1).

Outcome/Prognosis:

Response to immunosuppressive therapy is slow, taking weeks to months to take effect (7). In a retrospective study of 13 dogs with PRCA, the median time to see a 5% increase in PCV was 38 days, and the median time for PCV to return to reference range was 118 days. In the same study, all of the patients that were responsive to immunosuppressive therapy were able to be tapered off the medications except for two patients that relapsed after tapering off. Of the two that relapsed, only one required life-long treatment of every other day prednisolone. (7)

According to one source, non-regenerative anemias generally tend to have a worse prognosis than regenerative anemias (1). However, another study suggests that the prognosis of PRCA is “equivalent to or better than that for dogs with regenerative and nonregenerative immune-mediated anemia” (7). Due to limited data, interpretation of prognosis should be made with caution.

Conclusion

Pure red cell aplasia is characterized by a severe non-regenerative anemia with bone marrow biopsy showing depletion of erythroid precursors. Secondary causes must be ruled out before immune-mediated destruction is diagnosed. Treatment involves immunosuppressive

therapy with response taking several weeks. Prognosis is usually good, with most patients staying in remission once tapered off immunosuppressive medications.

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