

CLINICAL APPROACH TO CANINE IMMUNE-MEDIATED ANEMIA

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Immune-mediated hemolytic anemia (IMHA) is one of the most common causes of anemia in dogs. IMHA may present as an idiopathic event (primary) or secondary to a variety of infectious diseases, neoplasia, drugs, vaccines or inflammatory process (Table 1). There is no single pathognomonic finding for primary IMHA. Therefore, a diagnosis algorithm was proposed including the following criteria(1):

- Anemia: PCV usually less than 25-30%
- Evidence of immune-mediated destruction (≥ 2 signs): spherocytes; positive saline test without washing; positive Coombs' test (or flow cytometry)
- Evidence of hemolysis (≥ 1 sign): hyperbilirubinemia, significant bilirubinuria or icterus without functional hepatic disease, post-hepatic cholestasis or sepsis; hemoglobinemia; hemoglobinuria; erythrocyte ghost
- Elimination of underlying diseases that may cause anemia

INFECTIOUS DISEASE	<ul style="list-style-type: none"> • Ehrlichiosis/Anaplasmosis • Babesiosis • Mycoplasma hemocanis • Leptospirosis • Dirofilariosis • Histoplasmosis
NEOPLASIA	<ul style="list-style-type: none"> • Lymphoma • Hemangiosarcoma • Lymphocytic leukemia • Gastric and pulmonary carcinoma • Diffuse sarcoma
DRUGS	<ul style="list-style-type: none"> • Trimethoprim-sulfa or other sulfanamides • Penicillin • Cephalosporins • Levamisole • Phenylbutazone • Dipyrone • Chlorpromazine • Vaccines

DIFFERENTIAL DIAGNOSTICS

Identifying and eliminating diseases that cause IMHA may attenuate or stop immune-mediated erythrocyte destruction, which will allow to avoid adverse consequences of long-term immunosuppressive treatment. For similar reasons, non-immune causes of hemolytic anemias

need to be considered, for instance rare hereditary disorders (ex: PK or PFK deficiency), toxins (ex: zinc, acetaminophen, onion/garlic), severe hypophosphatemia (ex: DKA) and microangiopathic hemolytic anemias (ex.: heartworms, vasculitis, vascular and GI tumors).

HISTORY AND CLINICAL PRESENTATION

Predisposed breeds include English Spaniels, Poodles, Irish Setters and Collies, with American Cocker Spaniel representing nearly a third of idiopathic IMHA cases. Most studies show a higher prevalence in females. The average age is 6 years, but IMHA has been reported in dogs of all ages. Seasonality (spring and summer) has been suggested in some studies.

Clinical signs parallel the severity and progression of the anemia. Clinical presentation often includes collapse, weakness, exercise intolerance, lethargy, anorexia, tachypnea or dyspnea, vomiting, diarrhea and sometimes polyuria/polydipsia. Physical examination typically reveals pale mucous membranes, tachypnea, splenomegaly, hepatomegaly, icterus, pigmenturia (hemoglobinuria or bilirubinuria), fever and lymphadenopathy. A grade II-III/VI systolic murmur is frequently noted in dogs with a PCV < 20%. Petechiae, ecchymosis and melena may be present if the concomitant thrombocytopenia is severe.

DIAGNOSTIC

Complete blood count (CBC)

To evaluate the degree of anemia, a spun PCV is suggested because calculated hematocrit may be unreliable when agglutination is present.(1) Typically, patients with IMHA have a moderate to severe, highly regenerative, anemia. Blood smear evaluation allows the identification of signs of regeneration, including reticulocytes, polychromasia, anisocytosis and nucleated RBC. However, nearly one-third of dogs with IMHA are presented with a poorly regenerative anemia.

Spherocytosis is identified in 89-95% of cases of IMHA. Because they are rounded, spherocytes appear smaller and darker than normal RBC with a lack of central pallor. Although their presence is not considered pathognomonic for IMHA, marked spherocytosis is certainly very suggestive of the disease.

Neutrophilic leukocytosis with a left shift is also frequently encountered in dogs with IMHA.

When severe, leukocytosis is suggestive of tissue necrosis secondary to anemic hypoxia.

Approximately 50-70% of dogs with IMHA have concomitant thrombocytopenia caused by Evans syndrome (immune destruction) and/or DIC (reported in 45% of dogs with primary IMHA).

Finally, a blood smear may also allow identification of infectious agents (ex: Mycoplasma hemocanis, Ehrlichia and Babesia).

Saline test

A positive saline test is reported in 50-90% of cases of IMHA, and is associated with a higher mortality rate.

Direct antiglobulin test (Coombs test)

The sensitivity of the Coombs test is reported to be between 60-90%; therefore, a negative Coombs test does not exclude a diagnosis of IMHA. Flow cytometry is an interesting alternative, with sensitivity reported between 67-100%, and specificity of 87.5%.(1)

Coagulation assays

Because of the risk of DIC and thromboembolisms, coagulation times (PT and PTT) and platelet count are among the basic diagnostic tests for all patients with suspected IMHA. Evaluation of fibrin degradation products, d-dimer, thromboelastography can help with diagnosis.

Bone marrow aspiration/biopsy

Aspiration and biopsy of the bone marrow are particularly important in patients with non-regenerative anemia or additional cytopenia (i.e. thrombocytopenia or leukopenia).

Serology and/or PCR testing for infectious agents & Imaging

The definitive exclusion of infectious or neoplastic causes requires a thorough investigation through imaging (abdominal ultrasound and thoracic radiographs) and screening for infectious diseases, based on geographical localization and travel history.

TREATMENT

The success rate of therapy ranges from 40-70% with frequent relapses. The mortality rate ranges from a low 26% to almost 60% depending on the studies. In spite of this variability, the majority of publications agree on the main cause of death, i.e. thromboembolic diseases.

Blood transfusion

About 70-90% of IMHAs will require one or several blood transfusions. Packed RBC (pRBC), ideally no older than 7-10 days, are usually preferred when available given the normovolemic state of the anemia.(3) Increasing age of pRBC was associated with increased risk of mortality in dogs with hemolysis (90% had IMHA) and of hemolytic transfusion reaction.(4, 5) The decision to transfuse should ultimately be based on the patients clinical signs (e.g. tachypnea, tachycardia and weakness), but most dogs with a PCV < 15% will require blood transfusion.

Prior to transfusion, blood typing for DEA 1 should be performed in addition to crossmatching if previous transfusions were administered ≥ 4 days ago (or unknown transfusion history).

Persistent autoagglutination can preclude interpretation of blood typing and crossmatch; if present, washing RBC may allow compatibility testing to be performed.

Immunosuppressive therapy

To be noted that the ACVIM consensus statement recently proposed a treatment algorithm for IMHA.(3)

Glucocorticoids:

Glucocorticoids remain the cornerstone of IMHA therapy. Their mode of action is to reduce RBC destruction by inhibiting phagocytosis of antibody-coated RBCs and reducing the production of cytokines and immunoglobulins. A typical starting dose of prednisone is 2-3 mg/kg PO daily, or 50-60 mg/m²/day for dogs > 25 kg. Dexamethasone can also be used on a temporary basis, but it is essential to remember that it is 7 to 8 times more potent than prednisone (the dose should therefore be reduced accordingly). Unless the side effects are unacceptable, the glucocorticoid dose should not be decreased until the patient's PCV has stabilized close to normal values, with improvement in disease activity indices (e.g. spherocytosis, agglutination, serum bilirubin concentration and reticulocyte count). Once IMHA is stabilized for 2-3 weeks, the glucocorticoid dose can be reduced by 25% every 2-4 weeks. Unfortunately, glucocorticoids are associated with numerous side effects that can frustrate the owners and compromise the quality of life of the patient: polyuria / excessive polydipsia, almost obsessive polyphagia, incontinence and excessive

panting. More serious complications of the therapy include secondary infections, steroid-associated myopathy, and gastrointestinal ulcers.

Other immunosuppressants:

Additional immunosuppressive agents should be administered if glucocorticoids alone fail to induce remission, cause significant side effects, or fail to control IMHA unless given consistently at high doses. In addition, additional immunosuppressive drugs should be considered at the onset of IMHA in severe cases: presence of marked persistent autoagglutination, intravascular hemolysis, or non-regenerative anemia. The most commonly used immunosuppressive agents in dogs are azathioprine, cyclosporine and more recently mycophenolate mofetil(6, 7).

Cyclophosphamide, in combination with prednisone, was associated with decrease therapeutic success. Leflunomide, human intravenous immunoglobulin and splenectomy have been used in refractory cases with variable success rates.

Anticoagulant

A significant proportion of patients with IMHA will die from complications related to coagulation (DIC and mostly venous thromboembolism).(8) All dogs with IMHA, except those with severe thrombocytopenia (platelet count < 30 000/ul)(3). Based on the pathophysiology of venous thromboembolism, using anticoagulants (ex.: heparin, LMWH or rivaroxaban) +/- antiplatelet therapy may be preferred for thromboprophylaxis, particularly during the first 2 weeks after diagnosis when the risk of thrombosis is greatest. The ideal anticoagulant (or ideal combination) is unknown. Low dose aspirin (30% dogs with "aspirin resistance"), clopidogrel, heparin, low molecular weight heparin or rivaroxaban are all options to consider.(9, 10)

PROGNOSIS

Several laboratory findings have been associated with increased mortality rates in the short or long term(11-13). This led to the development of the Canine Hemolytic Anemia Objective Score (CHAOS), which was recently re-evaluated and was positively associated with mortality during hospitalization and at 30 days.(13) The latter includes the following parameters: age of the animal (> 7 years), temperature (> 38.9°C), presence of autoagglutination, albumin (<30 g / L), hyperbilirubinemia (> 85 µmol / L).

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