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Antibody and/or complement-mediated destruction of circulating RBCs is known as immune-mediated hemolytic anemia (IMHA). The immunological destruction occurs by a classical type II hypersensitivity reaction. This involves extravascular phagocytosis of opsonized RBCs in the spleen or liver; or intravascular osmotic lysis following the generation of terminal membrane attack complexes of the complement pathway (1). The antibodies originate due to immune dysregulation or cross reaction and can be directed against unaltered (primary or idiopathic IMHA) RBC membranes. In secondary IMHA, a stimulus for antibody production is present. Possible underlying causes or triggers include acute or chronic bacterial infections (e.g., leptospirosis, sepsis, ehrlichiosis, anaplasmosis), viral and parasitic diseases (e.g., babesiosis, leishmaniosis, dirofilariosis), lympho- and myeloproliferative neoplasias (e.g., lymphoma), drugs (e.g., sulfonamides, anticonvulsant drugs), vaccination, or incompatible blood transfusions. IMHA may be part of a multisystemic autoimmune syndrome (e.g., systemic lupus erythematoses). IMHA and immune-mediated thrombocytopenia may occur concurrently in approximately 30% of the cases (Evans’ syndrome).

In a few cases, antibodies can also be directed against RBC progenitor cells within the bone marrow and can cause a nonregenerative IMHA or pure red cell aplasia (PRCA) (8,10).

Primary IMHA occurs more frequently in certain dog breeds and families, such as Cocker Spaniels, and somewhat more frequently in female rather than in male dogs. Dogs of all ages are affected (2).

Signs of IMHA vary depending on the class of antibodies involved and the severity of hemolysis. In addition to signs of anemia, other signs such as anorexia, bilirubinuria, hemoglobinuria, icterus, or sometimes vomitus, diarrhea, fever, spleno- or hepatomegaly, and signs of an underlying disease can be present. Severe complications are disseminated intravascular coagulation (DIC), thromboembolic disease; hemorrhage, dyspnea (in cases of pulmonary thromboembolism), and multiorgan dysfunction.
Typical laboratory findings of IMHA include macroscopic or microscopic (persistent) RBC agglutination, numerous spherocytes, or a positive direct Coombs’ test (direct antiglobulin test). However, these findings do not necessarily occur simultaneously, neither do they occur in all cases, and they do not serve to distinguish between primary and secondary IMHA. The Coombs’ test can be positive as long as several weeks after initiating glucocorticoid therapy (2). A mild to severe regenerative anemia is present (reticulocytosis, nucleated RBCs, polychromasia, increased MCV). However, in as many as 30 % of the cases, anemia is nonregenerative at initial presentation (due to acute stage of disease, nonregenerative IMHA or PRCA). The osmotic fragility of RBCs is increased. Frequently, a severe leukocytosis (left shift neutrophilia) is present. Thrombocytopenia can occur due to DIC or in cases of Evans’ syndrome. Recent studies using thrombelastography revealed that hypercoagulability occurs in 85% of the dogs in the initial phase (6). Up to 65% of dogs develop DIC during the course of disease (7). Abnormalities of clinical chemistry and urinalyses include hyperbilirubinemia, increased liver enzymes, bilirubinuria or hemoglobinuria. Acute phase proteins (e.g., C-reactive protein) are elevated and may be useful for monitoring response to treatment (3). In order to differentiate between primary and secondary IMHA a complete history and a careful search for underlying diseases are important. Further examinations include blood smear examination (e.g., for babesia, blasts, morulae), serology/PCR tests (e.g., for babesiosis, anaplasmosis, ehrlichiosis, leptospirosis, leishmaniosis, dirofilariosis, hemoplasmosis), diagnostic imaging, (e.g., to exclude neoplasias), or a platelet-bound antibody or antinuclear antibody test if Evans’ syndrome or SLE is suspected.

Therapy of IMHA can be divided into three phases: (1) induction of remission, (2) maintenance therapy & prevention of relapse/complications, and (3) management of relapses.

1. Induction of remission

In secondary IMHA, drugs have to be discontinued if possible and underlying diseases have to be treated.

In cases of severe anemia (Hct < 0.16 – 0.18 l/l) a blood-type compatible blood transfusion (packed RBCs, whole blood, bovine hemoglobin) is indicated. Fresh blood products should preferably be used. Crystalloid infusions provide rehydration and might prevent complications such as DIC or thromboembolism. Antibiotic treatment is indicated because of immune dysregulation and therapeutic immune suppression. If a vector-borne disease (e.g., anaplasmosis) is suspected, doxycycline (5 mg/kg BID) is administered.

Prednisolone is the immunosuppressive drug of choice (1 – 1.5 mg/kg BID; higher dosage for smaller dogs); dexamethasone is rarely used (initially 0.6 mg/kg PO, IV, followed by 0.2 mg/kg). Glucocorticoids interfere with the expression and function of Fc receptors on macrophages and thus reduce phagocytosis of RBCs. Moreover, glucocorticoids can reduce antibody binding, and also complement activation and cytokine production. Since the Hct can decrease rapidly, the Hct has to be controlled once or twice daily. It can take up to two to three weeks to control hemolysis.

Other drugs which might be used for initial stabilization are human immunoglobulins (0.5 – 1 g/kg IV over 4-6 h), mycophenolate mofetil (10-20 mg/kg BID), or liposome-encapsulated clodronate (11).

In order to prevent thromboembolism unfractionated heparin, low molecular weight heparin or a ultra-low dose aspirin (0.05 mg/kg PO) have been used. It has not been established yet if clopidogrel given alone or in addition to aspirin is superior to aspirin alone. Individually adjusted dosing with unfractionated heparin (according to the anti-Factor Xa activity) was superior compared to constant low-dose unfractionated heparin (150 IU/kg SC q6h) (5). Unfractionated heparin can also be administered at a dosage of 250 IU/kg IV or SC
q6h, with the dosage being adjusted to PTT.

2. Maintenance therapy and prevention of relapses / complications

After response to therapy, the prednisolone dosage is carefully reduced by approximately 1/4- 1/5 every two weeks, and finally switched to dosing only every other day. After six months, discontinuation of prednisolone can be tried if no relapse has occurred. Because of the risk of gastrointestinal ulceration omeprazol (1 mg/kg BID) and/or sucralfate (20-40 mg/kg BID) are indicated. Further side effects of prednisolone include polyuria/polydipsia, incontinence, polyphagia, muscle loss, panting, behavioural changes, a cushingoid habitus, calcinosis cutis, predisposition for bacterial infections (e.g., of the urinary tract), increased risk of thromboembolism and possibly pancreatitis.

In severe cases or in cases of a relapse, the following adjunct immunosuppressive agents can be administered (initial dosages): cyclosporine (5 mg/kg BID), leflunomide (3-4 mg/kg SID), azathioprine (2 mg/kg SID), cyclophosphamide (50 mg/m2 4 d/week), or mycophenolate mofetil (MMF) (10 – 20 mg/kg BID) (11). However, there is no consensus as to which combination is most efficacious. Because of the myelosuppressive side effects of these drugs a CBC has to be performed every 1-2 weeks.

In individual cases, splenectomy may be considered as therapy for refractory patients. Disadvantages include the high risk of anesthesia and surgery in these dogs, an increased susceptibility to infections, and the risk of relapse due to the activity of the hepatic mononuclear phagocytic system.

Careful monitoring should be performed for at least 6 months after an episode of disease and at intervals for the lifetime of the animal.

3. Management of relapses

If a relapse, i.e. a decrease of the Hct, occurs the cause for the relapse has to be investigated thoroughly. Prior to initiation of the induction protocol complications such as gastrointestinal hemorrhage or infectious diseases have to be excluded. If not already administered adjunct immunosuppressive drugs should be given in addition to prednisolone. Medication should be tapered off very carefully; it is also possible that the patient may have to stay on a lifelong low maintenance dosage.

Prognosis is good for secondary IMHA if the underlying disease can be treated or if triggering factors can be removed. Prognosis is guarded for primary IMHA. Mortality rate in referral settings can be as high as 30-50% during initial hospitalization (4,9). Negative prognostic factors are autoagglutination, intravascular hemolysis, nonregenerative IMHA, severe leukocytosis, thrombocytopenia, high serum urea and bilirubin concentrations, increased liver enzymes, hypoalbuminemia, prolonged PT and aPTT, and DIC. The highest mortality rate occurs in the first 2 weeks after diagnosis. Most patients die within the first or second week. The relapse rate is high at percentages of 13-33% (4).

Comprehensive information of the owners and their compliance is very important for acute and long-term management.
References