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Review Article

REVIEW ON IMMUNE MEDIATED HAEMOLYTIC ANEMIA

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Introduction

IMHA can be either primary (idiopathic or autoimmune) or secondary. Primary IMHA, a classic autoimmune disorder with no recognised underlying cause, is the most frequent form of IMHA in dogs. The condition typically affects young adult and middle-aged animals, and is most common in cocker spaniels, English springer spaniels, poodles, and old English sheepdogs. IMHA can also occur secondary to a wide range of infectious, inflammatory or neoplastic processes. Important causes of secondary IMHA in small animals include Feline Leukemia Virus (FeLV) or hemobartonellosis (mycoplasmosis) in cats, and recent vaccination or neoplasia (particularly lymphosarcoma) in dogs [1]. Various medications have also been reported to trigger IMHA. Secondary IMHA affects animals of any age or breed, and should be strongly suspected in patients with a signalment atypical for primary IMHA, such as geriatric animals. Unlike the dog, IMHA in the cat is most commonly secondary. Distinction between primary and secondary IMHA is therapeutically important because secondary IMHA will often respond poorly to treatment, or recur, unless the underlying cause is recognized and eliminated [2]. There are two broad forms of IMHA: the subacute to chronic form, where there is a history of slowly progressive inappetance and exercise intolerance, and initial treatment is on an out-patient basis using prednisone [3]; and the basic causes, diagnosis and treatment is the focus of this review.

Etiology and pathophysiology

Immune-mediated hemolytic anemia (IMHA) arises when an immune response targets directly or indirectly erythrocytes and hemolytic anemia ensues. In primary IMHA no inciting cause can be identified, hence the term idiopathic IMHA or autoimmune hemolytic anemia (AIHA). In contrast, secondary IMHA is associated with an underlying condition or triggered by an identifiable agent [4]. The various breed and family predilections (about ⅓ of

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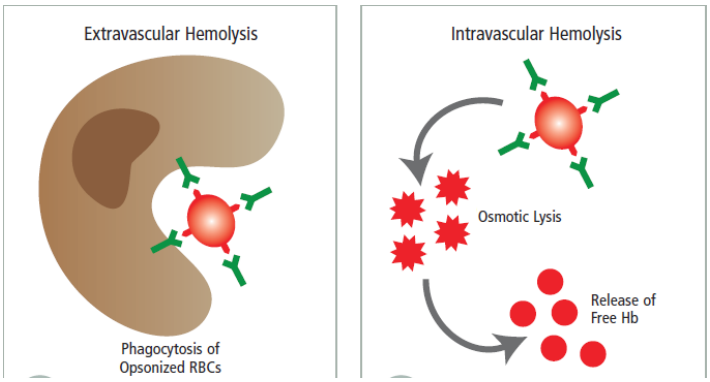
all cases of IMHA are seen in American Cocker Spaniels) suggest strongly the involvement of genetic factors leading to a predisposition to IMHA. There is ample evidence for infectious agents to be associated with IMHA, including parasitic (babesiosis, leishmaniasis, ehrlichiosis, and dirofilariasis), fungal, and bacterial (leptospirosis, chronic abscesses, discospondylitis, pyometra, colitis, and pyelonephritis). The relationship between infection and autoimmunity may be explained by molecular mimicry [1-3]. Furthermore, several drugs and toxins (e.g. sulfonamides, beesting) and neoplastic disease processes have been associated with IMHA.

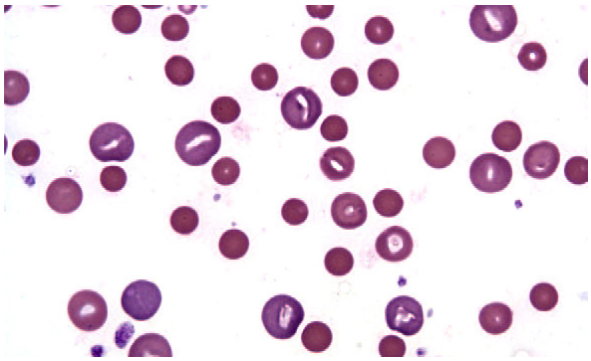
IMHA results from antibodies binding to red cells. Extravascular hemolysis occurs when macrophages in the macrophages in the spleen or liver phagocytose and remove the antibody or complement coated the RBC's [5]. Whereas C.J. PIek also stated that the intravascular hemolysis occurs when antibody and complement mediated lysis of RBC's occurs inside the circulation resulting into release of free hemoglobin into the plasma (Fig.1). Alternatively, macrophages may only phagocytize part of the RBC membrane, creating a spherocytes.

Figure 1: Pathophysiology of IMHA



(Photo courtesy: Michael J.Day (2012). Canine immune mediated haemolytic anemia Consultant on call. NAVC'S clinician brief)

Large numbers of spherocytes are pathognomonic for IMHA and they are eventually removed from the circulation by the liver and spleen. IgM-mediated RBC destruction occurs as part of a complement fixation process causing intravascular hemolysis [6]. This leads to weakening of the RBC membrane, water influx into the cell, and cell rupture within the blood vessels (intravascular hemolysis). Hemoglobin escapes into the plasma and is taken up by macrophages or bound to haptoglobin. In IMHA patients with intravascular hemolysis, these haemoglobin scavenging systems are rapidly saturated which leads to the development of hemoglobinemia and hemoglobinuria (port-wine colored urine).



Recent study stated that the most common immunoglobulin type involved in primary IMHA is IgG, followed by IgM along with variable involvement of complement [7]. The period of acute hemolysis is associated with a systemic inflammatory response. IMHA may be primary, or secondary to another disorder or treatment [8]. When a cause cannot be found, IMHA is assumed to be primary, which is the most frequent diagnosis.

Clinical Signs

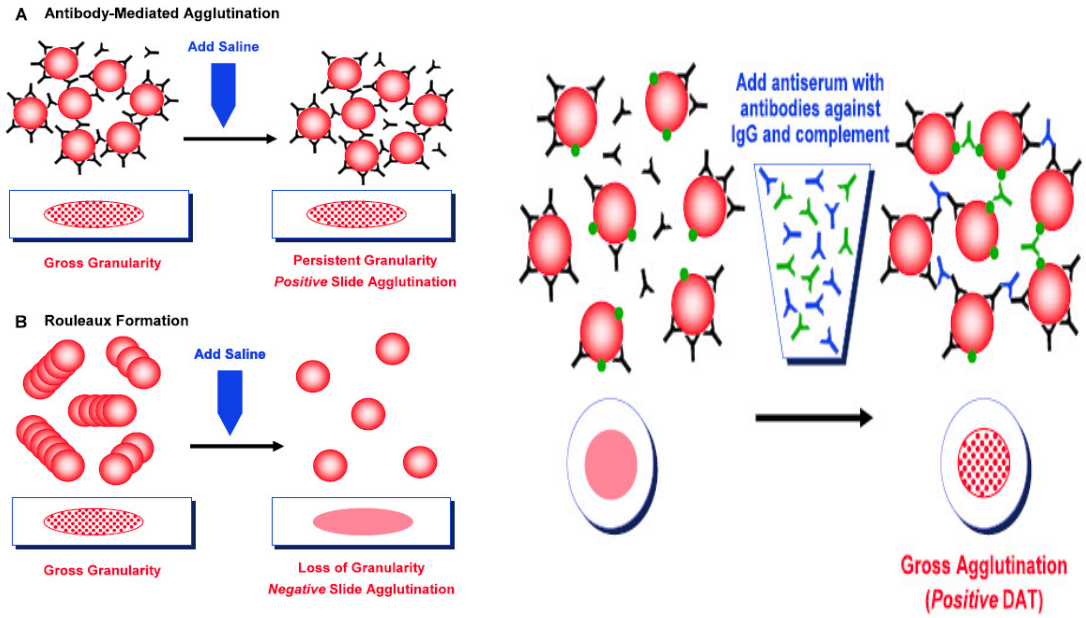
Signs typically associated with IMHA reflect the presence of both anemia (lethargy, weakness, pale mucous membranes, and a hemic heart murmur) and compensatory responses caused by tissue hypoxia [5, 7, and 9] and stimulation of the sympathetic nervous system (tachypnea, tachycardia, and bounding pulses). Some patients may also show clinical signs of an ongoing immunological or inflammatory process, such as pyrexia, anorexia and, uncommonly, lymphadenopathy. Surprisingly, since the MPS within the spleen and liver is usually the main site of RBC destruction, organomegaly is only variably present in animals with IMHA [10].

Patients with IMHA of acute onset tend to be very severely affected by their anemia, and are often very depressed, weak or even collapsed. Hyperbilirubinemia, bilirubinuria and tissue jaundice are often seen during acute severe episodes of IMHA [11]. Since intravascular hemolysis is uncommon, hemoglobinemia and hemoglobinuria are observed infrequently. Patients with extravascular hemolysis due to sub-acute or chronic IMHA can compensate to some extent for their lack of erythrocytes, and may be remarkably bright despite the presence of severe anemia [12]. In these patients, the liver can often cope with the extra bilirubin released by RBC breakdown, and jaundice does not occur. Pulmonary thromboembolism (PTE) is a well-recognised complication of IMHA, and is particularly common in those animals with acute severe anemia that are receiving high dose glucocorticoids [13]. Pulmonary thromboembolism should always be suspected in those anemicpatients that suddenly develop severe and persistent dyspnea, although other causes of dyspnea such as

cardiogenic pulmonary edema or acute bacterial pneumonia should also be considered, especially in dogs already receiving glucocorticoid and immunosuppressive therapy. Disseminated intravascular coagulation (DIC) can also complicate IMHA, but clinically significant DIC is probably uncommon to rare [14].

Diagnosis

A diagnosis of IMHA must demonstrate accelerated immune destruction of erythrocytes. Evidence of a hemolytic anemia is suggested clinically by icterus and a regenerative anemia with hyperbilirubinuria, and hemoglobinemia and hemoglobinuria refers to an intravascular process [15]. However, the erythroid response in the bone marrow may be blunted by the immune process or the underlying disease thereby leading to non-regenerative anemias. Beside documenting a hemolytic anemia, one or more of the following three hallmarks must be present to support a diagnosis of immune-mediated hemolysis: persistent agglutination, marked spherocytosis and a positive direct Coombs test result [16].



(Photo courtesy: Andrew Mackin, Immune mediated haemolytic anemia: pathophysiology and diagosis DVAVM 2014)

Treatment

Because the severity of IMHA ranges from indolent to life-threatening disease, therapy has to be tailored for each patient and depends in part, on whether the IMHA is primary or secondarymin nature [17]. Removal of the triggering agent or treatment of the underlying condition can bring the IMHA rapidly under control. Restoration and maintenance of tissue perfusion with crystalloid fluids is important even when it results in further lowering of the

hematocrit. When severe anemia and a dropping hematocrit result in signs of tissue hypoxia, packed cell transfusions appear beneficial.

The increased oxygen-carrying capacity provided by the transfused red blood cells may be sufficient to maintain the animal's hematocrit for a few days while other treatment modalities have time to become effective [18]. The notion that transfusionspose an increased hazard to animals with IMHA has been overemphasized and is not supported by recent retrospective clinical studies. However, the common occurrence of autoagglutinationmay make blood typing and cross matching of the patient impossible [6,10]. In these cases DEA 1.1 negative blood should be transfused. If compatible blood is not available, the bovine hemoglobin solution Oxyglobin may be administered and provides increased oxygen carrying capacity and plasma expansion [19]. In contrast to blood and Oxyglobin, oxygen inhalation therapy is of little benefit, unless the animal is suffering form pulmonary disease such as pulmonary thromboemboli.

Adequate transfusion support, animals with IMHA rarely die because of anemia, but because of secondary complications such as thrombo-emboli and infections [20]. The insufficient understanding of the pathogenesis, the generally guarded prognosis, the lack of good therapeutic trials, the serious drug side effects, and the high costs of intensive care greatly hamper the successful management of dogs with IMHA [5,12,14].

The main goal of immunosuppressive therapy is to reduce phagocytosis, complement activation, and anti-erythrocytic antibody production. Glucocorticosteroids are the initial treatment of choice for canine and human IMHA. They interfere with both the expression and function of macrophage Fc receptors [21] and thereby immediately impair the clearance of antibody-coated erythrocytes by the macrophage system. In addition glucocorticoids may reduce the degree of antibody binding and complement activation on erythrocytes, [22] and only after weeks, diminish the production of auto-antibodies. Thus, oral prednisone at a dose of 1-2 mg/kg twice daily is the mainstay treatment. Alternatively, oral or parenteral dexamethasone at an equipotent dose of 0.2-0.4 mg/kg twice daily can be used, but is likely not more beneficial [23].

Additional immunosuppressive therapy is warranted when prednisone fails, only controls the disease at persistently high doses, or when corticosteroids cause intolerable side effects [24-26]. They are generally used together with prednisone, but may eventually be used independently. Historically, cytotoxic drugs such as cyclophosphamide were added, however a small randomized study and several retrospective surveys failed to show any

beneficial effects, but may be associated with greater morbidity and mortality in the acute management of IMHA. Retrospective studies and anecdotal reports with azathioprine, cyclosporine,danazol, mycophenylate, leflunomide and human intravenous immunoglobulin indicate some efficacy and may be associated with fewer side effects, but controlled prospective clinical trials that document their efficacy and safety are lacking [27].

Response to therapy may be indicated by a hematocrit that rises or stabilizes, an appropriate reticulocytosis, diminished autoagglutination, and fewer spherocytes; this response can be expected to be seen within days [28]. The subsiding of autoagglutination would allow the performance of a Coombs' test and thereby permit the direct documentation of anti-erythrocytic antibodies. As glucocorticosteroid therapy is associated with well-known side effects, the initial dose will be tapered by reducing the amount by one-third every 7-14 days. In secondary IMHA with appropriate control of the underlying disease, the tapering can be accomplished more rapidly [29]. Because of the potential of gastrointestinal ulceration by steroids, gastrointestinal protectants such as sucralfate may be considered. Because dogs with IMHA suffer from an immune deregulation which may have been triggered by an infections and are treated with immunosuppressive agents, these patients are prone to experience infections; it is, therefore, prudent to administer preventative as well as therapeutic antibiotics to these dogs with IMHA on immunosuppressive therapy.

Thromboemboli and DIC are unique serious complications that greatly contribute to the morbidity and mortality of dogs with IMHA. Although the pathogenesis remains unknown, venopuncture, catheters, and glucocorticosteroids as well as other immunosuppressive agents may be contributing factors [30]. Thus far, no study has documented any successful preventionand/or management protocol for these lifethreatening hemostatic problems in canine IMHA.

Predisposing factors should, whenever possible, be limited, and adequate perfusionand tissue oxygenation should be provided with fluids and transfusions or Oxyglobin [31-33]. Generally, anticoagulation therapy is instituted after there is some evidence or suspicion of thromboemboli. Heparin is the most commonly used drug and is used at a dose of 50-250U/kg sc every 6 hours or by continuous infusion. The replacement of coagulation factors and antithrombin III has not been proven to be beneficial [34]. Other antithrombotic agents such as aspirin, low molecular weight heparin and novel antithrombotic agents have been used occasionally, but their efficacy and safety remain unproven.

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