IMHA

Immune-mediated hemolytic anemia, autoimmune hemolytic anemia, AIHA

Which Pets Can be Affected by IMHA?

Dogs of all ages may be affected with immune-mediated hemolytic anemia (IMHA). Young to middle-aged female dogs are thought to be affected more commonly with immune-mediated disease than their male counterparts. Older dogs often have underlying or concurrent problems when IMHA develops. In some dogs, IMHA can be caused by cancer, chronic infection or other ongoing inflammation in the body. Breeds including cocker spaniels, poodles, Old English sheepdogs, Lhasa apsos, and Shih-tzus may have a higher incidence of IMHA than other breeds.

IMHA is very rare in the cat.

Overview

The immune system normally helps to protect the body from outside invaders. However, it can become active against normal cells or parts of the body, or against normal cells that have been altered by exposure to infectious agents, medications, or other disease processes in the body. Although a variety of factors may be associated with the development of IMHA, in most situations it occurs without an identifiable trigger or underlying cause. This is referred to as idiopathic immune-mediated hemolytic anemia. “Idiopathic” means that we really do not understand what causes it.

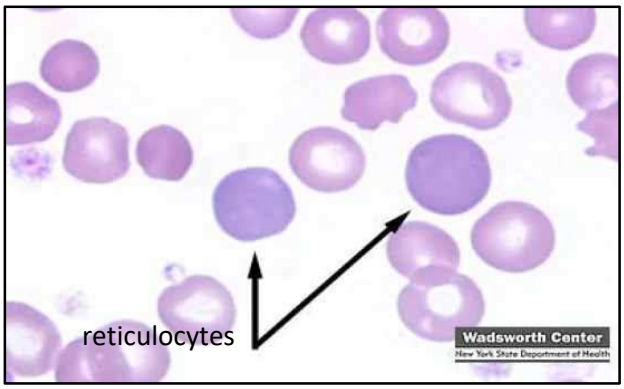
In immune-mediated hemolytic anemia, red blood cells are removed from the blood stream by the immune system. This can happen by destruction of the red blood cell right inside the blood vessels, or by removal of the red blood cells from the blood stream by organs such as the liver and spleen, or by both mechanisms. Veterinarians believe that antigens, or foreign substances in the body, alter red blood cell membranes and stimulate the immune system to eat up the red blood cells by mistake. When the process occurs inside the blood, it is called intravascular hemolysis, and when it occurs in the spleen liver, and sometimes other places in the body outside the blood stream, it is called extravascular hemolysis. “Hemolysis” is the medical term for destruction of the red blood cells. “Intra” means inside, and “extra” means outside.

What Are the Symptoms of IMHA?

The common signs associated with anemia include lethargy, weakness and paleness (pallor) of the tongue, gums and other mucous membrane surfaces which are normally a healthy pink. Many patients with immune-mediated hemolytic anemia have a recent history of nonspecific signs that can include poor appetite and vomiting. Changes in breathing patterns are common, and can range from panting to difficulty breathing, especially if a blood clot has formed in the lungs (pulmonary thromboembolism). The presence of yellow mucous membranes and skin (jaundice) in an anemic animal is highly suggestive of immune-mediated hemolysis as a cause of the anemia. Dogs with IMHA may present to the veterinarian collapsed or in shock. In situations where the anemia develops rapidly, signs can be severe, with some animals actually presenting to the veterinarian in shock. In other cases, especially when the targeted red blood cells are in the bone marrow rather than in circulation in the blood vessels, the onset can be very slow and gradual.

How is IMHA Diagnosed?

Anemia is diagnosed by documenting the presence of decreased red blood cells. This is most commonly done in the hospital with measurement of a packed cell volume (PCV) or hematocrit (HCT), which is often part of the Complete Blood Count (CBC). For all intents and purposes, PCV and HCT are just about equivalent. A complete blood count will also help reveal underlying causes for hemolytic anemia. Red blood cell parasites that can cause hemolysis may sometimes be seen on evaluation of a blood smear.



Anemias may be classified as regenerative and non-regenerative. Regenerative anemias arise when the red blood cells are being lost from the body or somehow destroyed by the body. Non-regenerative anemias occur because the bone marrow is not making sufficient numbers of red blood cells. “Reticulocytes” are immature, developing red blood cells. A reticulocyte count tells how many immature red blood cells are in circulation, telling us whether the anemia is regenerative or non-regenerative. In order to treat any significant anemia intelligently, we must understand the degree of regeneration. Most dogs with IMHA show a highly regenerative response, with increased reticulocyte counts. The most common causes of regenerative anemias are blood loss and hemolysis. Hemolysis should be suspected if there is a regenerative anemia with no evidence of internal or external blood loss. There are rare forms of IMHA that have low reticulocyte counts, because the destructive immune response is directed against the cells in bone marrow that make red blood cells. This form of immune-mediated, non-regenerative anemia, is sometimes referred to as “pure red cell aplasia.”

The most specific red blood cell change in IMHA is the formation of spherocytes, which are small, round-looking red blood cell that lacks the typical zone of paleness in its center when examined on a blood smear. Red blood cell auto-agglutination, or clumping, may be noted when blood is collected from dogs with IMHA. The presence of auto-agglutination is usually thought to be specific for IMHA, but its absence does not rule it out. Auto-agglutination may be either macroscopic, which means visible to the naked eye, or microscopic, indicating it can only be noted when drops of blood are examined under a microscope.

Changes in the white blood cell and platelet counts may be seen in addition to red blood cell count abnormalities on a complete blood count. Some dogs with IMHA have drastic increases in their white blood cell counts. This occurs when all cell lines within the bone marrow are excessively stimulated. Other dogs with IMHA may have decreased platelet counts, particularly if the immune-mediated injury involves platelets as well as red blood cells. This is called Evan's syndrome, and may be associated with a worse outcome in most patients than with IMHA alone.

Blood tests in dogs with IMHA often show non-specific changes. Serum bilirubin levels are increased due to excessive red blood cell breakdown, resulting in jaundice. Liver enzymes may be elevated; this occurs when anemia causes the liver to receive a decreased amount of oxygen. Protein levels are usually normal to increased in hemolytic anemia. This is a key point in distinguishing hemolysis from blood loss, since protein levels are usually decreased in blood loss situations.

Once anemia has been documented, there are many tests that are useful in further classifying the anemia. These tests may also help differentiate IMHA from other types of anemia. Chest and abdominal x-rays and abdominal ultrasound may be used to screen for evidence of cancer in older dogs with suspected IMHA. Cancer, especially lymphosarcoma, is often associated with immune-system abnormalities such as IMHA. Abdominal x-rays may also be useful in identifying zinc-containing foreign objects like coins, which can induce hemolytic anemia in dogs which have nothing to do with the immune system. Tests for tick-borne infectious diseases may need to be considered as well. Bone marrow evaluation may be recommended in some cases of non-regenerative anemia.

There is no single test that is absolutely diagnostic for immune-mediated hemolytic anemia. It is usually diagnosed based on suspicion and the absence of any other specific causes for anemia. Thorough testing prior to treatment is helpful to rule out underlying or associated conditions, to identify additional abnormalities that require treatment, and to monitor for complications of the disease and its treatment. When IMHA has been tentatively diagnosed, when no likely underlying cause has been identified by additional testing, and when there is no history of recent drug or vaccine exposure that may have triggered the event, the condition is often referred to as autoimmune hemolytic anemia, or AIHA, which is one type of IMHA. It is assumed in these cases that for unknown reasons, the immune system targets otherwise normal red blood cells, and tries to remove them from circulation.

What Causes IMHA?

There are many possible triggers for the development of IMHA. Exposure to certain medications that may alter the red blood cell membranes, or serve as a stimulus for antibody production against the red blood cells. Red blood cell parasites may either attach to the red blood cell membranes or invade the red blood cells directly, triggering an immune

response. Several Infectious diseases, such as ehrlichiosis and leptospirosis may be associated with IMHA. Some forms of cancer, particularly lymphosarcoma, can serve as triggers for IMHA. However, in most patients, there is no identifiable trigger or obvious underlying, associated condition. This situation is referred to as auto-immune hemolytic anemia (AIHA), which is one type of IMHA. The exact cause of this syndrome and the mechanisms that perpetuate it are not completely understood. In these patients, some abnormality in the immune system allows for the destruction of otherwise normal red blood cells. Veterinarians believe that there may be a hereditary predisposition to this condition. It may occur alone or in conjunction with other immune-mediated disorders is a disease complex that is referred to as Systemic Lupus Erythematosis, or "lupus" for short.

How is IMHA Treated?

Treatment of IMHA is aimed at restoring red blood cell numbers and trying to stop the ongoing destruction of additional red blood cells. Underlying causes or predisposing factors, when present, need to be addressed. If medications were being used prior to the diagnosis, they may be stopped, in case they may have triggered the problem. Transfusions may be needed in severely ill dogs, but are generally useful only as a temporary measure, allowing time for medications to take effect. A large number of drugs have been used to suppress the immune response in dogs with IMHA.

Treatment usually begins with high doses of corticosteroids, such as prednisone, prednisolone, dexamethasone or others. Most are aware that these medications carry side effects. However, the side effects must be balanced against the life-saving benefits. Without corticosteroids given for at least some period of time, almost all patients with IMHA will die.

Additional drugs to suppress or modify the immune system are commonly used to treat IMHA. It is thought that combination therapy may be more effective in some patients, and that it may limit side effects from over-reliance on a single class of drugs. These drugs have the potential to cause serious side effects, such as liver injury or bone marrow suppression, so patients must be carefully monitored, usually with regular blood testing. Examples of these drugs include azathioprine, cyclophosphamide, cyclosporine, mycophenolate, and others. Melatonin is a supplement that may help with treatment in some cases. It is very safe, but almost never controls the problem when used alone. Sometimes, an IMHA patient needs to take 3-5 or more of these medications that suppress the immune system at the same time, in order to get the problem under control. Once controlled, the patient will be weaned off drugs very slowly over a minimum of 3-6 months.

Despite a relatively large number of treatment options and treatment protocols with these medications, there is no one agreed upon, universally effective treatment for IMHA. All possible treatments have potential side effects that need to be carefully monitored, and once an animal is successfully managed through an initial crisis, long-term treatment is usually necessary. Many visits to the vet over months to years are often required in order to successfully treat this serious condition.

In some IMHA-patients that have failed to adequately respond to medical treatment, surgical removal of the spleen (splenectomy) may also be considered. This invasive step is seldom performed, although there are some reports that indicate it can be associated with a high degree of success. Because many patients with IMHA are in such critical condition, the risk of general anesthesia may be too high. As well, if IMHA is caused by an undetected underlying blood parasite such as Babesia, splenectomy could be fatal.

What is the Prognosis for IMHA?

There is an extremely wide range of severity of the condition, as well as an unpredictable response to treatment. Some animals are saved with relatively non-aggressive treatment and monitoring, while others succumb despite almost heroic efforts. As we mentioned above, IMHA is a very serious disease. On average, 40-50% of patients with IMHA are thought to die either from the disease itself, or from complications of IMHA and/or its treatment. Some factors that may be associated with greater likelihood of a poor outcome include severe jaundice, lower PCV/HCT at the time of diagnosis, the need for multiple transfusions, and the occurrence of pulmonary blood clots. Only an attempt at treatment will help determine the outcome in an individual dog. Those dogs that respond rapidly and favorably to treatment may do very well. Other dogs may require hospitalization for days to weeks before it becomes clear if they will survive.

If successfully treated, many survivors of IMHA never have a problem with again. However, if IMHA relapses, each episode can become more severe and more difficult to control than the last. For this reason, immunosuppressive drugs which have controlled the problem will be withdrawn every carefully and very gradually, and with close monitoring.

Can IMHA Be Prevented?

For most dogs with IMHA, there is no known means of prevention of the disease. Modified live-virus vaccinations may trigger IMHA in some dogs, so patients that are suspected of having had vaccine-related IMHA in the past probably should not be given these vaccines again. Some veterinarians recommend administration of no biological products at all, including any vaccine or even Cytopoint®, which is an antibody product used to control itching in allergic dogs.

References:

Celeste Clement, DVM ACVIM – Vetcentric.com
Wendy Blount, DVM - PracticalVetMed