Immune-mediated Hemolytic Anemia and Thrombocytopenia in the Dog: A retrospective study of 55 cases diagnosed from 1969 through 1983 at the Western College of Veterinary Medicine

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ABSTRACT

All recognized cases (n = 55) of immune-mediated hemolytic anemia and immune-mediated thrombocytopenia in dogs presented to the Western College of Veterinary Medicine from 1969 through 1983 were reviewed. Specific areas of concern were: association with other conditions, therapeutic response, prognosis, relapse rate and final outcome. Of these 55 cases, 19 were immune-mediated hemolytic anemia, 26 were immune-mediated thrombocytopenia and 10 were both immune-mediated hemolytic anemia and thrombocytopenia. Females were slightly over-represented and the mean age was 6.4 years. Therapy consisted of various combinations of immunosuppressive drugs and in some cases, whole blood transfusion and splenectomy. No firm conclusions could be made regarding therapeutic efficacy, as a result of variation in treatment protocol and the occasional unavailability of follow-up data. Well over half of all cases were diagnosed as idiopathic. Precipitating factors or diseases most frequently implicated in secondary immune-mediated thrombocytopenia or hemolytic anemia were: recent vaccination, drug therapy, obstetrical complications, stress, recent viral infection and neoplasia. Twice as many cases of immune-mediated hemolytic anemia were seen in the cooler months (October to March), although this could not be related to antibody class or thermal reactivity. Immune-mediated thrombocytopenia both as a single disease and combined with immune-mediated hemolytic anemia had no seasonal incidence. History, clinical findings and hematological and clinical chemistry findings were consistent with data previously reported, with the exception of icterus, which appeared to be of higher incidence than most reports, being present in almost 50% of immune-mediated hemolytic anemia cases. Just over half of all dogs survived, although the survival rate was highest for immune-mediated hemolytic anemia, followed closely by immune-mediated thrombocytopenia and lowest for the combined disease. Immune-mediated thrombocytopenia most frequently ran a relapsing course requiring long-term or intermittent therapy.

Key words: Immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, dogs, retrospective study.

RÉSUMÉ

Anémie hémolytique et thrombocytopénie auto-immunes, chez le chien

Cet article rapporte une étude rétrospective des 55 cas d'anémie hémolytique et de thrombocytopénie auto-immunes, diagnostiqués chez des chiens présentés au Collège de Médecine vétérinaire de l'Ouest, de 1969 à 1973. Les paramètres suivants retinrent particulièrement l'attention des auteurs : l'association à d'autres conditions, la réponse thérapeutique, le pronostic, le taux de rechute et l'issue finale. Des 55 cas précités, 19 correspondaient à de l'anémie hémolytique auto-immune; 26, à de la thrombocytopénie auto-immune et dix, à la présence simultanée de ces deux conditions. L'âge moyen des sujets impliqués dans cette étude se situait à 6,4 ans; les femelles étaient un peu plus nombreuses que les mâles. La thérapie consistait en diverses combinaisons de médicaments immunosuppresseurs et, dans certains cas, elle impliquait la transfusion de sang entier et la splénectomie. Il s'avéra impossible de tirer des conclusions définies concernant l'efficacité thérapeutique, à cause des variations du protocole de traitement et du manque de données relatives au suivi de certains patients. On diagnostiqua comme idiopathiques, plus de la moitié des cas. Les facteurs ou les maladies qui contribuèrent le plus souvent à l'éclosion de l'anémie hémolytique ou de la thrombocytopénie auto-immunes secondaires incluaient : une vaccination récente, une thérapie médicamenteuse, des complications obstétricales, un stress, une infection virale récente ou un néoplasme. Deux fois plus de cas d'anémie hémolytique auto-immune survinrent d'octobre à mars, en dépit de l'impossibilité de relier cette constatation à la classe d'anticorps ou à la réactivité thermique. La thrombocytopénie auto-immune, seule ou associée à l'anémie hémolytique auto-immune, ne présenta pas d'incidence saisonnière. L'anamnèse, les observations cliniques, hématologiques et biochimiques s'avérèrent compatibles avec les données déjà rapportées, à l'exception de l'ictère qui sembla plus fréquent que dans la plupart des rapports antérieurs, puisqu'il accompagnait au delà de 50% des cas d'anémie hémolytique auto-immune. Un peu plus de 50% des chiens survécurent; le taux de survie le plus élevé se recontra dans les cas d'anémie

hémolytique auto-immune; celui des cas de thrombocytopénie auto-immune le suivait de près. On enregistra cependant le plus faible taux de survie, dans les cas où les deux conditions précitées sévissaient simultanément. La thrombocytopénie auto-immune présenta très souvent des rechutes qui exigèrent une thérapie à long terme ou intermittente.

Mots clés: anémie hémolytique auto-immune, thrombocytopénie auto-immune, chiens, étude rétrospective.

INTRODUCTION

Immune-mediated hemolytic anemia (IHA) and immune-mediated thrombocytopenia (ITP) are diseases of Type II immunological injury. These result from the binding of IgG or IgM antibodies to antigenic determinants on the surface of the erythrocyte or platelet. Complement (C) may participate in the reaction (1,2). The affected blood cells are thus destroyed by intravascular lysis or phagocytosis by the monocyte-macrophage system (2,3,4,5,6,7,8). Immune-mediated hemolytic anemia and ITP are classified as either secondary or idiopathic according to the presence or absence of underlying disease. In dogs, 60 to 70% of cases have been classified as idiopathic (3,6).

Immune-mediated thrombocytopenia is less well studied or understood but shares many features with IHA. The anti-platelet antibody is of the IgG class although the pathogenic mechanism responsible for initiating and perpetuating ITP is still controversial. Because plasmapheresis causes remission in some patients, immune complexes of platelet fragments plus anti-platelet antibody attached to platelets may play a role in the pathogenesis of the disease, in addition to monocyte-macrophage phagocytosis and intravascular lysis (9,10).

The diagnosis of IHA is made based on history, physical findings, routine hematological findings, and the direct antiglobulin (Coombs') test. The diagnosis of ITP is made based on exclusion of other causes of thrombocytopenia until a sensitive assay to quantitate platelet-associated IgG (PAIgG) is available.

Therapy for both disorders consists mainly of corticosteroids, a variety of chemotherapeutic agents, and at times, splenectomy and blood transfusion. Despite the benefit obtained by many patients from vigorous treatment, some do not respond and some suffer frequent, occasionally fatal relapses. It would be desirable to know whether or not the available diagnostic techniques provide insight into the ultimate outcome of the disorder, particularly the results that can be expected from various types of therapy. Thus, the records of dogs with IHA and/or ITP seen at the Western College of Veterinary Medicine (WCVM) from 1969 through 1983 were studied and the findings are presented herein.

MATERIALS AND METHODS

Pertinent information from the records of the 55 affected animals was summarized to a standard format. If not available in the patient record, information on survival, relapse and therapeutic response was gained, where possible, through telephone communication.

The criteria for diagnosing IHA were:

1. anemia
2. regenerative response to the anemia
3. one of:
   3. spherocytes
   4. positive direct antiglobulin test
   5. autoagglutination
4. exclusion of other causes of anemia

The criteria for diagnosing ITP were:

1. thrombocytopenia
2. no leukopenia
3. exclusion of other causes of thrombocytopenia

Response to therapy was defined as a packed cell volume (PCV) of > 0.30 L/L for IHA and a platelet count of $> 100 \times 10^9$/L for ITP. The presence of icterus was based either on physical examination or visual assessment of the plasma. Splenomegaly or hepatomegaly was a clinical or radiographic finding. Lymphadenopathy was a clinical interpretation. Total red blood cell (RBC) count, total white blood cell (WBC) count, hemoglobin concentration, PCV and RBC indices were determined with an electronic cell counter (Coulter Model S, Coulter Electronics Inc., Hialeah, Florida). Leukocyte differential counts, RBC morphological features, reticulocyte counts and platelet counts were evaluated using standard techniques (11).

The direct antiglobulin test was performed during the period of 1969 to 1976 by adding a washed RBC suspension from the affected dog to rabbit anti-canine globulin serum (Supplied by the Sylvana Co. Inc., Millburn, New Jersey), incubating for 30 minutes at 37°C and examining grossly and microscopically for agglutination. From 1976 to 1977, a washed RBC suspension from the patient was added to each of anti-canine IgG, anti-canine IgM and anti-canine complement (C_3), and examined grossly and microscopically after 30 minutes at 37°C for agglutination. The specific antisera (Supplied by Dr. R.E.W. Halliwell, University of Florida, Gainesville, Florida) were previously adsorbed with washed canine RBC and tested for specificity by immunoelectrophoresis. In 1978, the test was done as described but at 24°C and 4°C in addition to 37°C. From 1978 to 1983, the test was performed using rabbit anti-dog IgG, goat anti-dog IgM and rabbit anti-dog C_3 (Supplied by Cappel Labs, West Chester, Pennsylvania) in serial dilution at 37°C, 24°C and 4°C.

Hematological values were recorded on day 1 (the day of admission) and when a low point for PCV and platelet count were reached. Survival referred to surviving the immune-mediated disease although death may have occurred from unrelated disease. Non-survival referred to death or euthanasia due to the immune-mediated disease or a related disease.

RESULTS

Clinical Features

Females were over-represented in the groups with IHA alone and ITP alone (Table I). Males were over-represented in the group with both IHA and ITP. In the same time period, 51% of all dogs presented to the WCVM were female. The age range and mean were similar in all three groups, with a peak in the middle years. There was no breed or size pre-

TABLE I
CANINE IMMUNE-MEDIATED HEMATOLOGICAL DISEASE: CLINICAL FEATURES

Category	IHA (n = 19)	IHA and ITP (n = 10)	ITP (n = 26)
Female	13	3	17
Male	6	7	9
Age Range (years)	1-12	2-11	1-11
Mean Age (years)	6.6	6.8	5.9
Diagnosed Oct.-Mar.	13	5	13
Diagnosed Apr.-Sept.	6	5	13

TABLE II
CONDITIONS ASSOCIATED WITH CANINE IMMUNE-MEDIATED HEMATOLOGICAL DISEASE

Factor	Number of Cases	Specific Features
IHA		
Recent[a] vaccination	2	1. Distempter, Hepatitis, Parvovirus Parainfluenza, Rabies 2. Distemper, Hepatitis, Rabies
Recent drug therapy	1	Griseofulvin
Neoplasia	1	Mastocytoma
Recent stressful episode	3	1. Ovariohysterectomy 2. Seizure activity 3. Professional grooming
IHA and ITP		
Recent vaccination	1	Distemper, Hepatitis
Recent viral infection	1	Parvoviral enteritis
Generalized illness	2	1. Vegetative valvular endocarditis 2. Systemic pyogranulomatous inflammation
Neoplasia	1	Pheochromocytoma
Recent stressful episode	1	Ovariohysterectomy
ITP		
Recent drug therapy	2	1. Sulfonamide 2. Sulfonamide and Penicillin G
Recent illness/infection	2	1. Upper respiratory inflammation 2. Hepatitis — Toxoplasmosis suspected (not confirmed)
Obstetrical complications	2	Overdue whelping followed by hemometra
Recent stressful episode	2	1. In boarding kennel 2. Ovariohysterectomy and cystotomy for leiomyoma
Multi-systemic immune-mediated disease	1	Systemic lupus erythematosus

[a]*Recent* refers to within two weeks prior to the onset of immune-mediated disease.

dilection. Cases in all three groups were diagnosed with increased frequency in the latter years of the study. Over twice as many cases of IHA were diagnosed initially in the cooler months (October to March); the numbers in the other two groups were evenly distributed over the cooler and warmer months.

Factors which may have contributed to the initiation of immune-mediated disease are listed in Table II. Seventy-five percent of IHA cases were classified as primary or idiopathic, as were 73% of cases of ITP and 60% of IHA with ITP. The clinical signs noted by the pet owners and findings reported on examination are listed in Tables III and IV.

Hematological Values (Table V)

All dogs with IHA were anemic on presentation and in many the severity increased over the following one to four days. The reticulocyte count was usually high, reaching a peak coincident with the nadir of PCV. Most dogs had a leukocytosis, consisting of a neutrophilia, elevated band response, and monocytosis, which also peaked with the nadir of PCV.

Most dogs with IHA and ITP were anemic on presentation and their disease tended to worsen for a variable period of time thereafter (1 to 30 days). The reticulocyte count tended to be highest on presentation and the platelet count often continued to drop for up to 14 days. A neutrophilia with a band response and monocytosis was greatest when the PCV was lowest.

Fifty percent of patients with ITP were not anemic on presentation although the platelet count was at or near its low point on admission. Many dogs had a mild neutrophilia, monocytosis, and left shift.

Direct Antiglobulin Test

The results of the direct antiglobulin test are shown in Table VII.

Treatment and Response

Prednisone was the most commonly used therapeutic agent for IHA, followed by cyclophosphamide, dexamethasone, vincristine, and azathioprine. Three of the 19 dogs were given whole blood transfusions. Of those that were treated, 69% responded and 14% relapsed. Response time, to attain a PCV of > 0.30 L/L, ranged from 7 to 35 days with a mean of 19 days. Of the three dogs that were given whole blood transfusions in addition to corticosteroids, one had an immediate rise in PCV with no subsequent drop; the second had an immediate rise in PCV followed by an equally rapid decline; the third died within one day with no further hematological studies. Patients with IHA were treated for 0 to 78 weeks with a mean of 13.2 weeks. There was an increased survival rate after four weeks of treatment.

Prednisone was the most commonly used drug for the group with both IHA and ITP, followed by vincristine, cyclophosphamide, azathioprine and dexamethasone. Four dogs were transfused

TABLE III
CANINE IMMUNE-MEDIATED HEMATOLOGICAL DISEASE:
SIGNS NOTED BY OWNERS
(IN DECREASING ORDER OF FREQUENCY)

IHA			
Anorexia			
Lethargy			
Weakness	— Red-brown urine	— Excessive water drinking	
Diarrhea	— Vomiting	— Not drinking	
IHA and ITP			
Blood in feces			
Lethargy	— Anorexia		
Weakness	— Blood in urine		
Not drinking	— Bleeding from mouth/nose	— Stiffness	
ITP			
Anorexia	— Bleeding from nose		
Blood in feces			
Bruises			
Lethargy			
Weakness			
Bleeding from mouth/vagina/eye			
Stiffness	— Blood in urine	— Bleeding from ears	— Diarrhea
Not drinking	— Abdominal pain		

TABLE IV
CANINE IMMUNE-MEDIATED HEMATOLOGICAL DISEASE:
FINDINGS ON PHYSICAL EXAMINATION
(IN DECREASING ORDER OF FREQUENCY)

IHA			
Pale mucous membranes			
Icterus			
Hepatomegaly			
Splenomegaly	— Fever	— Systolic heart murmur	
Tachycardia			
Dehydration	— Back pain		
IHA AND ITP			
Pale mucous membranes			
Intestinal bleeding (melena or frank blood in stool)			
Icterus			
Systolic heart murmur	— Petechiae	— Hepatomegaly	
Weakness	— Splenomegaly	— Lymphadenopathy	— Vaginal bleeding
	— Hematuria		
Hyphema	— Epistaxis		
ITP			
Ecchymoses	— Petechiae		
Ocular hemorrhage (hemorrhage into iris, subconjunctiva, sclera, retina or anterior chamber)			
Intestinal hemorrhage (melena or frank blood in stool)			
Systolic heart murmur			
Splenomegaly			
Pale mucous membranes			
Shock	— Abdominal Pain	— Lymphadenopathy	

and two were splenectomized. Of those treated, 90% responded initially but 75% of these subsequently relapsed; half relapsed with only ITP and half with both IHA and ITP. Response time for a rise in PCV ranged from 7 to 49 days with a mean of 21 days; and for platelets the response time, to attain a count of $> 100 \times 10^9$/L, ranged from two to ten days with a mean of seven days. Two of the four transfused dogs had a elevation in PCV with no subsequent decline. One of the four had an immediate rise in PCV which then dropped for two days before increasing again. The fourth dog returned to its original low level for PCV by the second day following the transfusion. The two splenectomized dogs responded only transiently and by the second postoperative day had returned to their presurgical platelet levels. Treatment periods ranged from 0.3 to 104 weeks, with a mean of 21.3 weeks. Survival was optimal with two to four weeks of treatment.

Prednisone was the most commonly used drug for the group with ITP, followed by vincristine, cyclophosphamide, azathioprine and dexamethasone. Five dogs were transfused and two were splenectomized. Of those treated, 79% responded initially and 41% of these later relapsed. The response time, to reach a platelet count of $> 100 \times 10^9$/L was 2 to 35 days with a mean of eight days. Of the six dogs given whole blood transfusions, one improved, one showed little change, three had an immediate rise in PCV followed quickly by a decline and death, and no record was available on the sixth dog. No record of response was available on the first splenectomized dog, however, it did have a recurrence of ITP. The second responded immediately, but returned to a low level by seven days. Patients were treated from 0 to 156 weeks with a mean of 20.6 weeks. Survival was lowest with $\leq$ one week of treatment, although long-term records were not maintained on 20% of the cases.

Outcome

The outcome on those cases in which records were available is presented in Table VII. Related diseases contributing to the death of or decision to euthanize patients were disseminated mastocytoma, disseminated intravascular coagulation, vegetative valvular endocarditis, pyogranulomatous lymphadenitis/hepatitis/glomerulonephritis, nonregenerative anemia and hepatic necrosis. One dog with ITP was later diagnosed as having systemic lupus erythematosus (SLE) and remains on treatment for that disease. Two dogs developed a severe nonregenerative anemia and leukopenia coincident with institution of therapy with azathioprine. Four dogs developed a mild nonregenerative anemia, one related to chronic vegetative valvular endocarditis, one

TABLE V
CANINE IMMUNE-MEDIATED HEMATOLOGICAL DISEASE:
HEMATOLOGICAL FINDINGS ON PRESENTATION

Parameter	Normal Range	IHA		IHA and ITP		ITP	
		Mean	Range	Mean	Range	Mean	Range
PCV (L/L)	0.37-0.55	0.21	0.11-0.33	0.23	0.08-0.40	0.33	0.15-0.48
Reticulocytes (%)	0-1.5	9.4	1.5-24.9	11.0	4.0-26.8	ND[a]	ND[a]
WBC ($x10^9$/L)	6.0-17.1	25.2	8.6-44.1	24.3	8.7-43.7	16.3	6.7-33.7
Bands ($x10^9$/L)	0.0-0.3	2.113	0-7.880	1.966	0-6.874	1.004	0-6.808
Platelets ($x10^9$/L)	200-900	OK[b]	OK[b]	18.5	10.0-30.0	17.0	0.5-66.0

[a]Not done
[b]Within normal limits

TABLE VI
CANINE IMMUNE-MEDIATED HEMATOLOGICAL DISEASE:
DIRECT ANTIGLOBULIN TEST RESULTS

Direct Antiglobulin Reaction	IHA (n = 19)	IHA and ITP (n = 10)	ITP (n = 26)
Positive (pooled)	3	0	1
Negative	6	5	9
Not Done	2	1	14
IgG	4	0	1
IgM	1	1	0
IgG, IgM, C_3	0	2	1
IgG, IgM	1	0	0
IgM, C_3	2	1	0

TABLE VII
CANINE IMMUNE-MEDIATED HEMATOLOGICAL DISEASE:
OUTCOME OF CASES ON WHICH RECORDS WERE AVAILABLE

Category	Died or euthanized due to this or related disease %	Died or euthanized due to unrelated disease %	Alive — on treatment for this or related disease %	Alive — not on treatment %
IHA	26	16	5	53
IHA and ITP	80	10	0	10
ITP	29	19	19	33

related to generalized mastocytoma and the other two for undetermined causes.

DISCUSSION

In man, a much lower percentage of cases of IHA and ITP are idiopathic (25 to 30% compared with 60 to 75% in dogs) (3,9). This reinforces the importance of thoroughly investigating canine cases for an underlying cause which may be of prognostic value.

The methodology for performing the direct antiglobulin test has changed over the years of study and therefore, comments concerning antibody class and thermal reactivity would be based on relatively few numbers. False negative results may occur due to failure of testing at a range of different temperatures and a failure of testing in serial dilution to avoid the problem of antiserum which is either too strong or too weak. Similarly, if steroid therapy were instituted prior to testing or if the anemia were in remission, the test result could be negative. False positive results can occur following whole blood transfusion and with incomplete adsorption of nonspecific antibodies from the antiglobulin (3,4,12).

Recommendations for treatment tend to reflect personal bias as no aspect of the management of these patients has been properly evaluated in a well-designed clinical trial. The use of corticosteroids to reduce the degree of phagocytosis and antibody production is reasonable and well accepted. Also with ITP, petechiae and purpura occasionally resolve on corticosteroid therapy before there is a rise in platelet count. A number of hypotheses have been proposed to explain this observation, including a reduction in capillary fragility, prednisone-induced amelioration of the endothelial thinning that accompanies thrombocytopenia, and the inhibition of endothelial synthesis of the naturally occurring antiplatelet agent, prostaglandin I_2 (3,7,10). The use of other immunosuppressive agents is more controversial. Therapy with cyclophosphamide or azathioprine has been reported to induce a drug-dependent remission in a variable number of human patients (7), but the numbers have been too low to allow conclusions concerning efficacy of treatment. Careful monitoring is essential when using these agents and even then, side effects can occur (3,5,9, 10,13). The Vinca alkaloids are often used to treat patients with ITP because of their effect of stimulating megakaryocytopoiesis and megakaryocyte fragmentation rather than their immunosuppressive properties; these may cause an immediate rise in platelet count and a reduction in the level of PAIgG, but this response is usually transient (10,14).

Similarly, the use of whole blood transfusion is controversial and may result in increased hemolysis and antibody production and suppression of the bone marrow response; however, in selected cases, it may be a lifesaving measure which lends more time for response to other therapeutic agents. Cross-matching is important, although with IHA, one must be satisfied with the match of least reactivity as a truly serocompatible donor is not possible (3,4). In this study, 5 of the 13 patients receiving whole blood transfusions improved. Retrospectively, it is not possible to determine if the transfusions aggravated the conditions of the remaining patients, or if they were beyond recovery prior to institution of therapy.

Splenectomy, in cases of IHA, should only be considered if the antibody is of the IgG class and reactive at 37°C and if more conservative forms of therapy have first been employed (15). If complement is involved or if the antibody is of the IgM class, phagocytosis occurs in the liver, therefore, splenectomy would be of little use (15). Similarly, for ITP, if the response to steroid therapy is poor, it is unlikely there would be a favourable response to splenectomy (10). There is an increased danger of septicemia in splenectomized people (9) and this along with Hemobartonellosis, is of concern in canine patients (11). There was only a transient response in the four dogs splenectomized in this study.

It must be recognized that IHA and ITP are serious diseases, the treatment of which requires owner compliance, thorough instruction and regular monitoring. Relapses occur, particularly with ITP, which can be frustrating for owners and clinicians. Because some of these cases become chronic, there is a tendency for follow-up records to be incomplete. This information is of importance if we are to learn more about therapeutic protocol and prognosis for these diseases. Also, the longer the cases are followed, the greater the possibility of determining an underlying cause (15). Results from this study indicate that IHA has the best prognosis for complete recovery. Patients with ITP most frequently require long-term therapy. The majority of patients with both IHA and ITP do not survive the disease and most commonly are found to have an underlying related problem. Although various tests have been described and some recent reports give promising results (1,16,17), a practical, sensitive, well-proven means for diagnosing ITP remains unavailable (10,15).

In conclusion, this study has revealed the current limitations in diagnosing and managing dogs with IHA and/or ITP. It has also served to reinforce the need for well-defined prospective studies to properly evaluate therapeutic protocols, the necessity of maintaining good records and follow-up data on affected patients and the importance of developing a good diagnostic test for ITP.

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