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Objective—To evaluate the clinicopathologic features, response to treatment, and risk factors associated with idiopathic neutropenia in dogs.

Design—Retrospective case series.

Animals—11 dogs.

Procedures—Medical records of dogs with idiopathic neutropenia were reviewed. Signalment, history, clinical signs, and response to treatment were recorded and compared with that in dogs with neutropenia attributable to known causes and to dogs without neutropenia (controls).

Results—Compared with dogs with neutropenia attributable to known causes, dogs with idiopathic neutropenia had lower neutrophil counts and were younger. When compared with control dogs, age < 4 years was identified as a risk factor for developing idiopathic neutropenia. In all dogs with idiopathic neutropenia, remission of neutropenia occurred within 18 days after administration of prednisone (2 to 4 mg/kg [0.9 to 1.8 mg/lb], PO, daily) and no serious complications or infections developed.

Conclusions and Clinical Relevance—An immune-mediated pathogenesis should be considered for dogs with idiopathic neutropenia in which the cause is not known. Severe neutropenia and young age were significantly associated with idiopathic neutropenia in dogs. Prognosis appeared to be excellent with prednisone treatment. (J Am Vet Med Assoc 2006;229:87–91)

Neutrophils are granulocytic cells produced in bone marrow that constitute an important part of the innate immune system. They are essential in initiating the immune response to invading pathogens, especially bacteria. Neutrophils also augment the immune response by releasing chemotactic substances, such as monocye chemotactic protein, that attract monocytes into tissues, decreased production of neutrophils by the bone marrow, or increased destruction caused by immune-mediated mechanisms. In a retrospective study evaluating quantitative neutrophil disorders in 261 dogs and cats, nonbacterial infectious disease (particularly parvovirus) was found to be the most common etiology. In that study, naturally occurring immune-mediated disease was the least common cause of neutrophil disorders, accounting for 0.38% of cases. Idiopathic neutropenia is poorly described in the veterinary literature. The first description of corticosteroid-responsive neutropenia in a dog was published in 1983. Since that time, only 4 reports that further describe the disease have been published. This is in contrast to the medical literature in humans, in which idiopathic autoimmune neutropenia is a well-recognized clinical disorder. The purpose of the study reported here was to evaluate the clinicopathologic features, response to treatment, and potential risk factors associated with idiopathic neutropenia in dogs.

Criteria for Selection of Cases

A computer search of the Veterinary Medical Database at Purdue University was performed, and all dogs in which a diagnosis of neutropenia had been recorded from January 1, 1990, through March 31, 2002, were identified. Medical records of 136 dogs admitted to the veterinary teaching hospitals at Purdue University and the University of Illinois with a diagnosis of neutropenia were reviewed. Inclusion criteria for the study included a diagnosis of a mature neutropenia on the basis of the lowest laboratory reference range of the 2 institutions (absolute neutrophil count < 3 × 10^3 cells/µL) and no identifiable cause of the neutropenia as determined by history and results of physical examination and diagnostic testing. Exclusion criteria included dogs with a diagnosis of drug-induced neutropenia; neutropenia caused by inflammatory diseases, sepsis, or myelophthisic bone marrow disease (leukemia, infiltrative neoplasia, myelofibrosis, and granulomatous myelitis); and parvoviral-induced neutropenia. Dogs

Disorders of neutrophils may result in persistent or recurrent infections, which can cause substantial illness and even death. Quantitative neutrophil disorders (neutropenia) develop secondary to increased margination and egress from the vascular compartment into tissues, decreased production of neutrophils by the bone marrow, or increased destruction caused by immune-mediated mechanisms.
in which inadequate data were available to sufficiently determine whether exclusion criteria existed were also excluded. Three (2%) records were not available for review and were excluded from the study. Eleven of the 153 (7%) remaining dogs met the inclusion criteria.

**Procedures**

Signalment and historical information including age at time of diagnosis, breed, sex, and weight as well as the owner’s initial complaint, duration of illness prior to referral, drug administration, and vaccination history were recorded. Results of initial laboratory tests performed at the veterinary teaching hospitals were recorded. Results of CBCs and serum biochemical analyses were included from the time of diagnosis. Neutropenia was defined as an absolute neutrophil count < 3.0 × 10^3 cells/µL. Results of concurrent laboratory tests were recorded from the initial visit and before specific treatment was instituted. Information obtained included results of cytologic examination of bone marrow aspirates, bone marrow core biopsy specimens, and lymph node aspirates; bacteriologic culture of lymph nodes; aerobic bacteriologic culture of urine; and aerobic and anaerobic bacteriologic culture of blood; cytologic examination and bacteriologic culture of samples obtained during arthrocentesis; serum IFA titers against *Ehrlichia canis, Ehrlichia platys, Babesia canis, Rickettsia rickettsii*, and *Borreia burgdorferi*; and cytologic analysis and aerobic bacteriologic culture of CSF samples.

Results of diagnostic imaging performed during the initial examination were recorded. Initial type and dosage of treatment were recorded as well as the duration from initiation of treatment to the first neutrophil count that was within reference range, if available. All concurrent medical treatment was also recorded.

**Statistical analysis**—Statistical analysis was performed by use of a commercially available software program. Age, weight, sex, neuter status, breed (purebred vs mixed breed), and laboratory findings (WBC count, neutrophils, band neutrophils, lymphocytes, monocytes, eosinophils, and basophils) in dogs with idiopathic neutropenia were compared with dogs that had neutropenia from known causes. Age, weight, sex, neuter status, and breed (purebred vs mixed breed) of dogs with idiopathic neutropenia were also compared with that in dogs without neutropenia (control dogs) that were randomly chosen from the population of dogs evaluated at the Purdue University Veterinary Teaching Hospital in the same year as dogs with idiopathic neutropenia at a ratio of 1 case dog to 10 control dogs.

Categoric variables were compared by use of a Fisher exact test or χ² analysis. Continuous variables were compared by use of a Kruskal-Wallis test. All variables with values of P < 0.20 were entered into 2 logistic regression analyses. One model was used to compare dogs with idiopathic neutropenia with dogs that had neutropenia from known causes, and a second model was used to compare dogs with idiopathic neutropenia with randomly chosen control dogs.

Logistic regression analysis was used to obtain odds ratios and 95% confidence limits for potential risk factors for idiopathic neutropenia. Values of P < 0.05 were considered significant.

**Results**

Eleven of 153 (7%) dogs met the inclusion criteria for idiopathic neutropenia. Breeds identified included mixed-breed dogs (n = 4) and 1 dog each of the following breeds: Dachshund, Toy Poodle, Yorkshire Terrier, Akita, Shih Tzu, Standard Poodle, and German Shorthaired Pointer. Body weight varied from 2.5 to 37.7 kg (5.5 to 83 lb; median, 10.0 kg [22 lb]). Eight dogs were females, and 3 were males. Ten dogs were neutered, and 1 female was sexually intact. Median age of dogs at the time of diagnosis was 4 years (range, 2 to 12 years old).

Duration from onset of illness prior to referral ranged from 3 to 180 days (median, 46 days). Persistent fever (n = 8) and lethargy (4) were the most common clinical signs. Other clinical signs included lameness (n = 2), anorexia (2), epistaxis (1), and facial edema (1). Treatment prior to referral included antimicrobials (n = 7), nonsteroidal anti-inflammatory drugs (3), corticosteroids (2), and antihistamines (1). Of dogs that received corticosteroids, 1 received triamcinolone acetonide (0.1 mg/kg [0.045 mg/lb], SC) 7 days prior to referral, and 1 dog received a single dose of dexamethasone (dose unknown) administered IV 5 days prior to referral.

Results of CBCs were available from the time of diagnosis for all 11 dogs. Total WBC counts were below reference range in all 11 dogs (median, 220 cells/µL [range, 406 to 4,800 cells/µL]; reference range, 6,000 to 17,000 cells/µL). Total neutrophils counts ranged from 0 to 2,380 cells/µL (median, 110 cells/µL). Band neutrophils were detected in 4 dogs (range, 80 to 190 cells/µL; reference range, 0 to 300 cells/µL). Lymphopenia was detected in 3 dogs. Monocytosis was detected in 1 dog, and monocytopenia was detected in 4 dogs. Eosinophil counts were < 100 cells/µL (reference range, 0 to 800 cells/µL) in 7 of the 11 dogs. Mild anemia was detected in 8 dogs; Hct ranged from 26.2% to 35.9% in those dogs (reference range, 37% to 55%). Mild thrombocytopenia was detected in 3 dogs (< 200,000 platelets/µL; reference range, 200,000 to 500,000 platelets/µL).

Results of serum biochemical analyses were available for all 11 dogs. Abnormalities included hyperglobulinemia (median, 3.9 g/dL [range, 2.9 to 4.6 g/dL]; reference range, 1.7 to 3.8 g/dL) in 5 dogs and increased alkaline phosphatase activity (median, 181 U/L [range, 64 to 1,174 U/L]; reference range, 20 to 157 U/L) in 9 dogs. No other severe abnormalities were detected. Prothrombin and activated partial thromboplastin times were reported in 4 of 11 dogs and were within reference limits.

Radiography of the thorax and abdomen was performed in 11 dogs. No abnormalities were detected on thoracic radiographs. Mild hepatomegaly was detected on survey abdominal radiographs in 3 dogs. Abdominal ultrasonography was performed in 5 of the 11 dogs (including each of the dogs in which hepatomegaly was detected on survey abdominal radiographs). In 1 dog,
ultrasonography of the abdomen revealed that the wall of the gallbladder was mildly thick (subjectively). However, no abnormalities were detected on cytologic examination and bacteriologic culture of bile samples obtained via ultrason-guided cholecystocentesis. Ultrasound-guided biopsy of the liver was performed in this dog; histologic examination of the biopsy specimen revealed moderate to marked extramedullary granulopoiesis. No growth was detected on aerobic bacteriologic culture of liver tissue.

Results of aerobic bacteriologic culture of urine were available for 10 of the 11 dogs; no growth was detected on any sample. Results of bacteriologic cultures of blood were available for 5 of the 11 dogs; no growth was detected on any sample. Cytologic examination of bone marrow aspirates was performed in all 11 dogs and revealed mild to marked myeloid hyperplasia in 9 dogs and moderate myeloid hyperplasia in 2 dogs. Bone marrow core biopsy was performed in 7 dogs, including the 2 dogs with myeloid hyperplasia seen on cytologic examination of bone marrow aspirates. In each dog, results of histologic examination of a bone marrow core biopsy specimen were similar to results of cytologic examination of bone marrow aspirates.

Results of cytologic examination of samples obtained via arthrocentesis were available for 3 dogs and were interpreted as normal. Cytologic examination of lymph node aspirates were performed in 7 dogs; results varied from nondiagnostic to reactive lymphoid hyperplasia. One dog had a detectable IFA titer (1:1,024; reference range, 0 to 1:4) against *R. rickettsii*.

Bacteriologic culture of lymph nodes was performed in 2 dogs, and no growth was detected on either culture. No abnormalities were detected on cytologic examination of CSF obtained from 1 dog, and bacteriologic culture of CSF from the same dog yielded no growth.

Nine of the 11 dogs had received antimicrobial treatment prior to administration of prednisone without resolution of clinical signs or neutropenia. Neutropenia was detected in each of those 9 dogs prior to administration of antimicrobials. Antimicrobials used included enrofloxacin (n = 8), amoxicillin (6), doxycycline (3), metronidazole (2), cefazolin (1), cephalaxin (1), and clindamycin (1). At the time an immune-mediated cause of the neutropenia was suspected, treatment with prednisone (2 to 4 mg/kg [0.9 to 1.8 mg/lb], PO, daily) was initiated in each dog. Duration of administration of corticosteroid treatment to detection of a neutrophil count that was within reference range was 1 to 18 days (median, 7 days). No other immunosuppressive medication was administered to any dog at any time.

Dogs with idiopathic neutropenia (n = 11) were compared with dogs in which neutropenia was attributable to known causes (77). When compared with dogs with neutropenia attributable to known causes, dogs with idiopathic neutropenia were significantly (P < 0.05) younger and had significantly (P < 0.01) lower neutrophil counts. Results of adjusted odds ratios for these risk factors also indicated that each increase of 100 cells/µL in neutrophil count was associated with a 14% decrease in the probability of developing idiopathic neutropenia (Table 1).

Odds ratios between control dogs and dogs with idiopathic neutropenia indicated that dogs < 4 years old were 4.1 times as likely to develop idiopathic neutropenia as dogs ≥ 4 years old (P < 0.05; Table 2). The remaining calculated odds ratios were not significant.

**Discussion**

Primary autoimmune neutropenia has been well described in humans. In 1973, Lalezari et al provided evidence that chronic neutropenia in an infant was caused by autoantibody against a neutrophil-specific antigen. Experimental studies in rabbits have shown that neutrophil-specific autoantibodies can cause neutropenia. Autoantibody against neutrophil-specific antigen was detected in 4 of the 11 dogs (Table 1). In 1989, Carbone et al described a case of autoimmune neutropenia in a dog in which the development of autoantibody against neutrophil-specific antigen preceded the occurrence of neutropenia. In 1990, Parks et al described a case of autoimmune neutropenia that developed in a dog in which neutropenia lasted 2 years. In 1998, Lalezari et al described 2 cases of autoimmune neutropenia in dogs in which neutropenia developed in association with malignant lymphoma. In 2002, Lalezari et al described a case of autoimmune neutropenia in a dog in which neutropenia was associated with an autoimmune reaction to *R. rickettsii.*

**Table 1**—Results of logistic regression analysis for potential risk factors for development of idiopathic neutropenia in dogs (n = 11), compared with dogs with neutropenia attributable to known causes (77).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Unadjusted Odds ratio</th>
<th>95% confidence limits</th>
<th>Adjusted* Odds ratio</th>
<th>95% confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>0.83</td>
<td>0.65, 1.01</td>
<td>0.91</td>
<td>0.75, 1.10</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.95</td>
<td>0.90, 1.00</td>
<td>0.97</td>
<td>0.91, 1.03</td>
</tr>
<tr>
<td>Neutrophils (per 100)</td>
<td>0.85</td>
<td>0.75, 0.97</td>
<td>0.96</td>
<td>0.79, 0.99</td>
</tr>
<tr>
<td>Lymphocytes (per 100)</td>
<td>1.03</td>
<td>0.99, 1.08</td>
<td>1.04</td>
<td>0.99, 1.10</td>
</tr>
</tbody>
</table>

*Adjusted for 3 remaining risk factors (ie, age, weight, neutrophil count, and lymphocyte count).

**Table 2**—Results of logistic regression analysis for potential risk factors for development of idiopathic neutropenia in dogs (n = 11), compared with dogs without neutropenia (control dogs; 110).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Unadjusted Odds ratio</th>
<th>95% confidence limits</th>
<th>Adjusted* Odds ratio</th>
<th>95% confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>2.10</td>
<td>0.80, 7.32</td>
<td>4.19</td>
<td>1.03, 17.10</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>3.89</td>
<td>0.80, 18.84</td>
<td>4.59</td>
<td>0.87, 24.12</td>
</tr>
<tr>
<td>Sex (male vs female)</td>
<td>2.97</td>
<td>0.75, 11.81</td>
<td>2.57</td>
<td>0.59, 11.29</td>
</tr>
<tr>
<td>Neuter status</td>
<td>5.27</td>
<td>0.65, 42.79</td>
<td>7.47</td>
<td>0.81, 68.83</td>
</tr>
</tbody>
</table>

*Adjusted for 3 remaining risk factors (ie, age, weight, sex, and neuter status).
neutropenia (a disorder of myelopoiesis), cyclic neutropenia, severe chronic neutropenia, and Felty's syndrome. Autoantibodies only by neutrophils. In addition, primary autoimmune neutropenia has been elucidated by demonstrating a fall in neutrophil counts as antibody titers increase and vice versa. In addition, primary autoimmune neutropenia has been distinguished from other causes of neutropenia, such as alloimmune neonatal neutropenia, severe chronic neutropenia (a disorder of myelopoiesis), cyclic neutropenia, and Felty's syndrome. Autoantibodies against members of the integrin family of cell adhesion proteins, specifically CD11b/CD18 and glycoprotein complex IIb/IIIa have also been detected. However, these autoantibodies are not neutrophil specific and have been detected in various clinical disorders, including immune-mediated thrombocytopenia, rheumatoid arthritis, and Coombs-positive hemolytic anemia.

In contrast, autoimmune neutropenia has been infrequently reported in the veterinary literature. To the authors' knowledge, only 9 dogs have been described as having corticosteroid-responsive, idiopathic neutropenia. The retrospective study reported here was designed to evaluate the clinicopathologic features and potential risk factors for idiopathic neutropenia in dogs.

Presently, there are no known neutrophil-specific antigen groups in veterinary species. Immunoglobulin G and C associated with promyelocytes and bone marrow neutrophilic elements have been detected via an immunofluorescent antibody test in 2 dogs suspected of having immune-mediated destruction of their neutrophils. Although this test does not distinguish between neutrophil-specific antigen and shared or adsorbed surface antigens, it does lend further support to an immune-mediated mechanism of disease. In our study, dogs were not tested for neutrophil-associated IgG and C3 because this test was not readily available. Elucidation of a neutrophil-specific antigen in dogs would permit further characterization of the pathophysiology and diagnosis of primary autoimmune neutropenia. An immune-mediated basis for development of idiopathic neutropenia was suspected in dogs in our study because of the lack of an identifiable underlying cause of neutropenia and the rapid and complete response to immunosuppressive medication.

In our study, dogs had nonspecific clinical signs; the most frequently reported being persistent fever. Other clinical signs included lethargy, lameness (often a shifting limb lameness), and anorexia. This is consistent with reports in humans with primary autoimmune neutropenia, who generally have mild bacterial infections. Fever of unknown origin is among the most common manifestation in humans as well as superficial pyoderma, otitis media, and upper respiratory tract infections. Severe infections, including pneumonia, sepsis, and meningitis, develop in approximately 17% of cases.

In our study, severe infections were not detected in dogs. One possible explanation is the differences among treatment modalities. All dogs in our study received prednisone (2 to 4 mg/kg, PO, daily) after an immune-mediated basis to their neutropenia was suspected. A range of 1 to 18 days elapsed before remission, and relapses were not detected as dogs were weaned from corticosteroid administration. In humans, treatment with corticosteroids is contraindicated, as the median age at diagnosis is 8 months.

Minor infections are treated with antimicrobials as they develop. If severe infections develop or surgery is necessary, temporary remissions may be achieved with corticosteroids, IV administration of IgG, and, more recently, granulocyte colony–stimulating factor. Spontaneous remission occurs in humans; median duration of disease is reportedly between 13 to 20 months. Because of the lack of considerable adverse effects of corticosteroid administration in adult dogs as well as the rapid response to prednisone administration, corticosteroids are typically used to achieve remission of disease. Whether spontaneous remission would occur in dogs similar to that seen in children with primary autoimmune neutropenia is not known.

Monocytosis is detected in 38% of human patients with autoimmune neutropenia. It is presumed that the body responds to infection with a monocytosis to compensate for the lack of neutrophils. A repeatable monocytosis was not detected in dogs in our study. This may have been associated with the duration of illness. In addition, lymphocyte counts were higher in dogs with idiopathic neutropenia than dogs with neutropenia from known causes. This is consistent with what is found in humans with primary autoimmune neutropenia, as their lymphocyte counts tend to remain greater than the upper reference limit. One possible explanation may be that the associated antigenic stimulation induces an increase in total lymphocyte count caused by chronic, persistent infections, which would be supported by the hyperglobulinemia detected in several dogs in our study. Although no infections were documented in the medical records of dogs included in our study, 9 of 11 dogs had been treated with antimicrobials prior to referral.

Neutropenia with an associated lymphocytosis has also been detected in dogs with experimental transmission of granulocytic ehrlichial organisms and in humans with Felty's syndrome and T-cell lymphotropic virus.
the study reported here, 1 dog had a detectable IFA titer against R rickettsii; however, the dog did not respond to administration of doxycycline (8 mg/kg [3.6 mg/lb], PO, q 12 h) for 7 days.

In the study reported here, dogs with idiopathic neutropenia had a significantly lower neutrophil count than dogs that had neutropenia attributable to other causes. This is also consistent with primary autoimmune neutropenia in humans, in which the neutrophil count is frequently < 500 cells/µL. The neutrophil counts in 4 of 9 dogs reported in the veterinary literature as having immune-mediated neutropenia were also < 500 cells/µL, and the neutrophil count of a fifth dog was < 500 cells/µL before treatment with prednisone was initiated. A disparity between the degree of neutropenia and the severity of clinical signs has been reported in humans and dogs with immune-mediated neutropenia. Reasons for this finding are not clear.

The combination of granulocyte immunofluorescence testing and granulocyte agglutination testing is recommended to reach a definitive diagnosis of primary autoimmune neutropenia in humans. Although an immune-mediated etiology was suspected for the 11 dogs in our study, these tests were not available for use in veterinary species. Therefore, dogs included in our study could not be definitively diagnosed with primary autoimmune neutropenia. As a result, the terminology ‘idiopathic neutropenia’ is tentative until specific neutrophil antigens are identified.

Idiopathic neutropenia is an uncommon disorder that should be included on the differential list of any animal with neutropenia in which the underlying cause for the neutropenia cannot be elucidated after thorough diagnostic investigation. In our study, dogs with idiopathic neutropenia were younger than control dogs and dogs in which neutropenia was attributable to known causes. Compared with dogs with neutropenia attributable to known causes, the neutrophil count of dogs with idiopathic neutropenia was significantly lower. Because of the significantly low neutrophil counts and marked response to prednisone treatment, an immune-mediated pathophysiology was suspected. On the basis of this small number of dogs, the prognosis should be considered good with appropriate corticosteroid treatment.

References
