Case Report Rapport de cas

Immune mediated neutropenia and thrombocytopenia in 3 giant schnauzers

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Abstract — Neutropenia, thrombocytopenia, and splenomegaly were recognized in 3 adult female giant schnauzers. Antineutrophil antibodies were demonstrated in 2 dogs. Following splenectomy, administration of prednisone and azathioprine resulted in normalization of neutrophil and platelet numbers in all dogs.

Résumé — Neutropénie à médiation immunitaire et thrombocytopénie chez 3 Schnauzers géants. Une neutropénie, une thrombocytopénie et une splénomégalie ont été diagnostiquées chez 3 femelles Schnauzer géants. Des anticorps antineutrophiles ont été observés chez 2 chiens. Après splénectomie et administration de prednisone et azathioprime, le nombre de neutrophiles et de plaquettes est revenu à la normale chez tous les chiens.

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Dog 1

A 4-year-old, 33 kg, spayed female, giant schnauzer was presented to the Small Animal Clinic at the Western College of Veterinary Medicine (WCVM) with a 7-day history of lethargy and decreased appetite.

Case description

Physical examination revealed pyrexia (39.8°C) and splenomegaly. A complete blood (cell) count (CBC) showed neutropenia (2.862×10^9/L; reference range, 3.6 to 11.5 $\times 10^9$/L), monocytosis (1.026×10^9/L; reference range, 0.08 to 1.0 $\times 10^9$/L) and thrombocytopenia (95×10^9/L; reference range, 200 to 900 $\times 10^9$/L). The hematocrit was 0.34 L/L (reference range, 0.370 to 0.550 L/L) with no evidence of red blood cell regeneration. Results from urinalysis were normal (USG 1.033, normal sediment) and urine culture for bacteria was negative. Serum biochemical values were normal, except for increased serum alkaline phosphatase (ALP) (179 U/L; reference range, 12 to 106 U/L). A CBC performed on Day 2 confirmed persistence of the neutropenia (2.401×10^9/L). Abdominal radiographs confirmed splenomegaly and abdominal ultrasonographs demonstrated that the spleen was enlarged and homogeneous with normal echogenicity. Thoracic radiographs were normal. A coagulation profile, consisting of prothrombin time (PT), partial thromboplastin time (PTT), and fibrin degradation products (FDPs), was normal. A Knott's test for heartworm was negative. A direct antiglobulin (Coombs') test was negative. Antinuclear antibodies (ANA) were not detected (< 1:40).

Cytologic examination of a bone marrow aspirate revealed megakaryocytic hyperplasia and an increase in early granulocytic precursors, with a relative depletion of post mitotic granulocytes. Marrow macrophage activity was greatly increased with extensive phagocytosis of erythrocytes and granulocyte nuclei.

A splenectomy was performed. Histopathologic examination of the spleen showed increased red pulp cellularity, marked extramedullary hematopoiesis, and increased macrophage activity with erythrophagia. A CBC performed 2 d postoperatively showed resolution of the neutropenia (5.760×10^9/L) and thrombocytopenia (250×10^9/L). Hematologic parameters were monitored weekly and remained normal for 1 mo postoperatively. Six weeks after surgery, the dog was again neutropenic (2.044×10^9/L), but the estimated platelet count was normal. Bone marrow examination revealed orderly and active megakaryopoiesis; granulopoiesis; and erythropoiesis, with markedly increased marrow macrophages engulfing nucleated erythrocytes; neutrophils; and platelets. Direct and indirect Coombs' tests were negative. Antineutrophil antibodies were demonstrated in the patient's serum by using an indirect agglutination test. Briefly, the serum of the patient was incubated for 30 min at 37°C with saline-washed buffy coat cells harvested from the patient's blood. The cells were then rewashed, incubated with antiserum to dog immunoglobulin (Ig)G, IgM, and complement factor 3 (C3) (Coombs' reagent), resuspended, and applied to glass slides. The cell smears were air-dried, stained with hematoxylin and eosin, and viewed with a light microscope. Serum from a normal dog was tested concurrently as a control. The serum of the patient, but not that of the normal dog, demonstrated agglutination of the patient's neutrophils. A tentative diagnosis of immune-mediated neutropenia (IMN) and thrombocytopenia was made and prednisone therapy (Apo-Pred;

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Apotex, Toronto, Ontario), 1 mg/kg bodyweight (BW), PO, q12h was initiated. There was resolution of the neutropenia within 5 d (10.726×10^9/L).

The dosage of prednisone was gradually decreased over a 2-month period and azathioprine (Imuran; GlaxoSmithKline, King of Prussia, Pennsylvania, USA), 2.2 mg/kg BW, PO, q24h, was added. During the next 4 y, the dog was reevaluated at least monthly and drug dosage adjustments were made to maintain the dog on the lowest possible doses of immunosuppressive drugs. Neutrophil numbers were stable when the dog was administered azathioprine, 1.5 mg/kg BW, PO, q48h, and prednisone, 0.75 mg/kg BW, PO, q48h. Attempts to further decrease the dose of either drug resulted in recurrence of neutropenia.

After 4 y of therapy, the dog was presented to the emergency service at the WCVM with an acute onset of bloody diarrhea, lethargy, and collapse. The dog was euthanized and a necropsy revealed torsion of the small intestine (jejunum) with severe congestion and necrosis.

Dog 2

An 8-year-old, 29.5 kg, spayed female, giant schnauzer was referred to the WCVM with a 2-week history of lethargy, decreased appetite, and mild generalized discomfort. A CBC performed on the day prior to referral revealed anemia (hematocrit 0.32 L/L; reference range, 0.37 to 0.55 L/L) and neutropenia with a left shift (neutrophils 1.31×10^9/L; bands 1.09×10^9; reference range, 0.0 to 0.3×10^9/L).

The dog had been treated for 4 y prior to presentation with levothyroxine (Synthroid; Abbott, Saint-Laurent, Quebec), 10 μg/kg BW, PO, q12h, in spite of having had a normal thyroid stimulating hormone response test result, because the owner felt that the dog exhibited behavioral and dermatologic signs of hypothyroidism that resolved with treatment. Post supplement thyroxine (T4) measurements were within the normal range. The 5th digit on the left forelimb had been amputated due to a squamous cell carcinoma 7 mo earlier. Diethylstilbesterol (DES; Eli Lilly, Indianapolis, Ohio, USA), 1.0 mg, PO, q24h for 4 d, then 1.0 mg, PO, q48h, for 2 wk, had been administered for urinary incontinence in the 2 wk prior to referral.

Case description

Physical examination revealed a depressed, febrile (39.5°C) dog in thin body condition. The right prescapular and right popliteal lymph nodes were enlarged, as was the spleen. A CBC confirmed anemia (hematocrit 0.32 L/L; reference range, 0.370 to 0.550 L/L), neutropenia (2.38×10^9/L), monocytosis (2.465), and left shift (bands 0.85×10^9/L). Results from a serum biochemical profile and urinalysis were normal.

Cytologic and histopathologic examination of a bone marrow aspirate and core biopsy revealed a hypercellular marrow with granulocytic hyperplasia and a myeloid:erythroid ratio of 4:1 (M:E reference range; 0.75 to 2.5:1). Megakaryocytes were present and maturation of all cell lines appeared orderly.

Thoracic and spinal radiographs were normal. Abdominal radiographs and ultrasonographs revealed diffuse, symmetrical splenomegaly. Examination of aspirates of the right prescapular, left popliteal, and right popliteal lymph node revealed reactive hyperplasia. Results from analysis of synovial fluid from both hock and carpal joints were normal. Three 10-mL blood samples were collected at 30-min intervals by alternating jugular veins and then submitted for aerobic and anaerobic bacterial culture, which failed to yield bacteria.

The dog was discharged with instructions to the owner to administer cephalexin (Novopharm; Scarborough, Ontario), 22 mg/kg BW, PO, q8h for 14 d, during which time the dog experienced some clinical improvement in attitude and activity. A CBC obtained on Day 5 was normal, but on Day 12 the neutropenia had worsened (1.428×10^9/L). Four days after the antibiotic treatment had finished, the dog was more depressed and was returned to the WCVM for further evaluation.

The dog was febrile (39.9°C) and very depressed. Splenomegaly and lymphadenopathy were unchanged. Results from a CBC revealed severe neutropenia (0.810×10^9/L) with a left shift (bands 0.765×10^9/L) and severe thrombocytopenia (20×10^9/L). Results from a serum biochemical profile, urinalysis, and urine culture were normal. Spinal radiographs and ultrasonographs of the spleen were unchanged. Cardiac ultrasonographs were normal. Results from an adrenocorticotrophic hormone (ACTH) stimulation test were normal. Antinuclear antibodies were present in serum at a titer suggestive of autoimmune disease (1:160). A direct antiglobulin test to detect antibody on the surface of neutrophils was nondiagnostic, due to low circulating neutrophil numbers. Prednisone therapy (Apo-Pred; Apotex), 2.2 mg/kg BW, PO, q12h was initiated.

Three days later (Day 21), the dog had improved clinically. Results from a CBC showed a return to normal neutrophil (7.82×10^9/L) and platelet (240×10^9/L) numbers. Antineutrophil antibodies were detected in the dog's pretreatment serum by performing an indirect agglutination test with the patient's posttreatment neutrophils, thus supporting a presumptive diagnosis of IMN.

The dog was anesthetized and the spleen and both prescapular lymph nodes were removed. Histopathologic examination revealed marked splenic hemosiderosis and congestion, and marked lymphoid hyperplasia of the lymph nodes. An incidental finding at the time of surgery was a small diaphragmatic hernia in the left dorsal diaphragm with the cranial pole of the spleen adherent to the diaphragm in this region. The hernia was repaired and the dog recovered uneventfully from surgery.

On the day after surgery, results from a CBC revealed neutrophilia (42.6×10^9/L). Prednisone (Apo-Pred; Apotex), 2.2 mg/kg BW, PO, q12h was administered for 7 d, after which the dose was decreased to 2.2 mg/kg BW, PO, q24h for 14 d and then to 2.2 mg/kg BW, PO, q48h. After 14 d of alternate day dosing, the dog was again neutropenic (3.12×10^9/L), so azathioprine (Imuran; GlaxoSmithKline), 2.2 mg/kg BW, PO, q24h was added to the prednisone therapy. The CBC remained normal on this medication.

Ten weeks following splenectomy, the dog was presented to the referring veterinarian with a 4-hour history of retching, dyspnea, and shock. A CBC was normal. Thoracic radiographs revealed a diaphragmatic hernia with herniation of the stomach into the thorax. Supportive measures were taken, but the dog died before specific therapy could be initiated.

Dog 3

An 8-year-old, 30 kg, spayed female, giant schnauzer was presented to the WCVM with a 2-day history of anorexia, lethargy, and ptyalism. The dog's previous history had included surgical repair of cranial cruciate ligament rupture in the left stifle 4 y earlier and in the right stifle 3 y earlier. Prior to this episode of illness, the dog had been systemically normal.

Case description

Physical examination revealed a depressed dog in good body condition. The dog was febrile (40.7°C) and tachypneic (66 breaths/min). Results from an oral examination were normal. The only abnormalities observed on physical examination were excessive salivation, splenomegaly, and mild submandibular lymphadenopathy.

A CBC revealed severe neutropenia (0.024×10^9/L) and thrombocytopenia (76×10^9/L) with giant platelets. The hematocrit was 0.371 L/L. Results from a biochemical profile showed a mild increase in ALP (182 U/L). The urinalysis was normal and culture of urine for bacteria was negative. Three 10-mL blood samples were collected aseptically at 30-min intervals from alternate jugular veins and then submitted for standard aerobic and anaerobic bacterial culture, results from which were negative. Results from a coagulation profile (PT,PTT, FDPs) were normal. Cytologic examination of lymph node aspirates revealed reactive hyperplasia. Thoracic radiographs were normal, and abdominal radiographs and ultrasonographs revealed a diffusely enlarged spleen with slightly increased echogenicity. Cytologic evaluation of fine needle splenic aspirates revealed extramedullary hematopoiesis of erythroid and megakaryocytic cell lines, with an increase in plasma cells and moderate erythrophagia.

Treatment was initiated with IV fluids (lactated Ringer's solution, 2 mL/kg BW/h) and cephalexin (Novopharm), 33 mg/kg BW, IV q8h. Cytologic examination of a bone marrow aspirate revealed megakaryocytic hyperplasia, normal cellularity and maturation of erythroid precursors, and granulocytic hypoplasia. Plasma cell numbers were slightly increased (3%; normal ≤ 2%) and moderate erythrophagia was noted. Serum testing for ANA was negative (< 1:40). A direct antiglobulin (Coombs') test was negative for IgG, IgM, and C3 at 37°C. Serum trypsin-like immunoreactivity (TLI), cobalamin, and folate were all normal.

After 4 d of antibiotic treatment there was no change in the dog's condition. Prednisone (Apo-Pred; Apotex), 1 mg/kg BW, PO, q12h, and azathioprine (Imuran; GlaxoSmithKline), 2 mg/kg BW, PO, q24h, were added to the ongoing antibiotic and fluid therapy. Within 12 h, the dog was bright and eating and the temperature was normal (38.1°C). On Day 7, a CBC revealed a hematocrit of 0.361 L/L, normal neutrophil numbers (4.690×10^9/L), and normal platelet numbers (221×10^9/L). Neutrophils from this sample were used to perform an indirect test for antineutrophil antibodies. Antineutrophil antibodies were not detected in either pre-or post-treatment patient serum, using post treatment neutrophils as targets and fluorescein-labeled anti-dog IgG in a flow cytometric method for detection of surface-bound Ig. The dog was discharged from the hospital and continued to do well clinically at home. Two weeks later, a CBC revealed a decreased hematocrit (0.297 L/L), normal neutrophil numbers (10.890×10^9/L) and decreased platelet numbers (86×10^9/L). The spleen was removed surgically and on histopathologic examination revealed moderate hemosiderosis and nodular hyperplasia.

One week postoperatively, neutrophils (16.653×10^9/L) and platelet (335×10^9/L) numbers were increased. During the next 6 wk, the prednisone dose was gradually tapered to 2 mg/kg BW, PO, q24h, but the azathioprine dose was continued at 2 mg/kg BW, PO, q24h. The dog was monitored weekly and did very well clinically. Neutrophil and platelet numbers remained normal, though the nonregenerative anemia persisted (hematocrit 0.249 L/L).

Seven weeks after splenectomy, the dog was presented again to the WCVM for a non weight bearing lameness on the left hind limb. There was moderate soft tissue swelling and synovial fluid distention of the left stifle. A CBC revealed a nonregenerative anemia (hematocrit 0.237L/L), normal neutrophil numbers (10.881×10^9/L) with increased bands (0.468×10^9/L) and normal platelet numbers (325×10^9/L). Synovial fluid from the swollen stifle had increased cellularity with nondegenerate and degenerate neutrophils, some containing gram-positive cocci or gram-negative rods. Culture of the synovial fluid yielded 1+ enterococcus and 1+ escherichia coli. The owner elected to have the dog euthanized.

Discussion

The 3 giant schnauzers in this report were only remotely related, with no shared relatives in 3 generations. The clinical and clinicopathologic findings in these dogs, as well as their response to therapy, are supportive of a diagnosis of IMN and thrombocytopenia.

Immune-mediated destruction is an uncommon cause of neutropenia in dogs. Neutropenia is more commonly caused by the shifting of neutrophils from the circulating pool to the marginal pool, as a result of marked inflammation (1–5) or ineffective granulopoiesis secondary to bone marrow injury by drugs, toxins, infectious agents, or neoplasia. A rare cyclic neutropenia of gray collies can occur as a lethal hereditary syndrome associated with gray-silver hair coloration (6). Mild neutropenia with hypersegmentation and stunted growth has been reported as an inherited disorder secondary to vitamin B12 malabsorption in immature giant schnauzers (7,8). No evidence for significant infection, overwhelming inflammation, neoplasia, drug or toxin exposure, stunted growth, or morphologic abnormalities of neutrophils was identified in the 3 dogs in this report.

Immune-mediated destruction of circulating neutrophils or neutrophil precursors in the marrow can be seen as a primary (idiopathic) syndrome, associated with systemic immune-mediated disease, or secondary to infectious agents, neoplasia, or drug administration. Primary IMN has been reported to account for less than 1% of all neutropenia cases in dogs (1,3). Immune-mediated neutropenia is diagnosed by exclusion of other causes of neutropenia and a favorable response to immunosuppressive therapy. Demonstration of antineutrophil antibody is required for definitive diagnosis, but this methodology is not widely

available. Two of the dogs reported herein had circulating antineutrophil antibodies demonstrated by using an indirect neutrophil agglutination method, attempts to demonstrate antibody in the 3rd dog by using flow cytometry were negative.

Immune-mediated neutropenia is the least well documented of the immune-mediated cytopenias. The 1st description of corticosteroid responsive idiopathic neutropenia in a dog was in 1983 (1,9); since that time, there have been only a few reports of apparent IMN (1–3,10,11). The most commonly reported clinical signs of presumed IMN in dogs are anorexia, lethargy, and fever (1). The neutropenia in dogs with IMN is usually more severe [median 100 polymorphonuclear neutrophils (PMN)/μL] than the neutropenia associated with other disorders (1,2,11). Affected dogs are generally young adults (median 4 y) and females are more commonly affected (1,2). Splenomegaly is rarely reported. Bone marrow examination typically reveals granulocytic hyperplasia, although granulocytic hypoplasia, as was seen in Dog 3, can be seen when antibodies are directed against granulocytic precursors (2,12). Neutrophil-associated IgG and C3 have been documented in a few dogs via immunofluorescent techniques. Immunosuppressive treatment generally resolves the neutropenia in dogs with IMN within 1 to 18 d (1,2,11).

In humans, primary idiopathic autoimmune neutropenia is a rare condition that usually occurs without alterations in other hematologic cells (12,13). The immune response can be directed against specific neutrophil membrane antigens or nonspecific surface antigens shared by other hematologic cells (1,12,14). Antigens specific for neutrophils first become apparent at the myelocyte stage of maturation and increase in number as the granulocytic cells mature (12). Autoantibodies of the IgG or IgM class result in opsonization of neutrophils in the circulation and maturing granulocytes in the marrow and cause accelerated removal of the cells by macrophages in the spleen, liver, lymph node, and marrow (12). In humans, IMN has been seen in association with systemic immune-mediated disorders, such as systemic lupus erythematosus (SLE), rheumatoid arthritis, and Felty's syndrome (12,13). Neutropenia occurs in more than 50% of humans with SLE and many more have demonstrable neutrophil-bound antibodies (8,13). Felty's syndrome is a triad of rheumatoid arthritis, splenomegaly, and granulocytopenia, where the spleen is the site of immune-mediated neutrophil destruction making splenectomy the preferred treatment (13,15).

Combined immune-mediated neutropenia and thrombocytopenia is rare in dogs. Approximately 25% of dogs and humans with idiopathic IMN have concurrent thrombocytopenia (2,9,10,16). Antibodies in these patients may be directed against cell surface proteins that are not specific to the neutrophil cell line (1). Concurrent destruction of neutrophils and platelets has also been reported in human patients with SLE, Felty's syndrome, and primary hypersplenism (16). Immune-mediated neutropenia and thrombocytopenia have been reported secondary to drug administration in humans, dogs, and cats (4,14,17).

Hypersplenism is a poorly described syndrome where hematopoietic cells are sequestered in an enlarged spleen, resulting in anemia, neutropenia, and thrombocytopenia with compensatory bone marrow hyperplasia (14,18). Splenectomy causes a complete and permanent resolution of pancytopenia in most affected humans (18). Splenomegaly has not been a prominent feature of dogs reported with IMN, but it has been reported in dogs with immune-mediated thrombocytopenia (IMT) (19). Although splenomegaly was pronounced in each of the dogs in this report and all experienced clinical improvement following splenectomy, ongoing immunosuppressive treatment was required to maintain normal neutrophil and platelet numbers.

Criteria for diagnosis of primary idiopathic IMT in neutropenic dogs typically include documentation of active bone marrow megakaryocyte production, no history of drug administration or testing to eliminate tick-borne diseases, disseminated intravascular coagulation, neoplasia, and SLE (19). Most dogs with IMT have very low platelet counts ($< 50\ 000/\mu L$) at the time of presentation but respond rapidly to immunosuppressive therapy (20,21). Splenectomy may be useful in the management of dogs with relapsing or refractory IMT (20).

Specific tests to document circulating antibodies against neutrophils are required for a definitive diagnosis of IMN, but these tests are not widely available and are rarely performed. The leukoagglutination test was the earliest and most widely used test to detect antineutrophil antibodies. In this test, patient neutrophils are incubated with patient serum and a smear is reviewed for agglutination (12,13). Immunofluorescence and immunocytochemical assays have also been used to detect antibodies bound to neutrophils (direct test) or in the circulation (indirect test) (2,13). In the dogs reported here, a modification of the indirect leukoagglutination technique was performed. Agglutination occurred after Coombs' reagent (antibodies directed against canine antibodies) was added to post-treatment neutrophils from Dogs 1 and 2 that had been incubated with pretreatment serum and then washed. This positive test, the failure to identify another cause to explain the neutropenia and thrombocytopenia, and the rapid response to therapy in all 3 dogs supported a diagnosis of immune-mediated disease.

Corticosteroid administration is advocated for the initial treatment of IMN and IMT to decrease antibody production and to prevent destruction of antibody-coated cells by macrophages in the spleen, liver, lymph nodes, and marrow. The response to therapy is typically rapid and complete. Concurrent administration of azathioprine is recommended when the response to corticosteroid is inadequate or if the dose of prednisone cannot be tapered without relapse. In dogs with IMT, treatment with prednisone and vincristine has been associated with a more rapid increase in platelet numbers and a shortened duration of hospitalization than treatment with prednisone alone (21), so this treatment should be considered in dogs with concurrent IMN and IMT. Splenectomy has been effective in the management of some dogs with relapsing or refractory IMT (20) and is used routinely in the treatment of refractory IMT and IMN in humans. Splenectomy was used together with chronic immunosuppressive therapy to manage the 3 dogs in this report. CVJ

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Contributors

C. Vargo reviewed the case records of each patient, reviewed the literature, wrote the original draft of the manuscript and modified the manuscript incorporating suggestions from the other authors.

S. Taylor managed 2 of the 3 cases as patients, acquired and interpreted the data, assisted in the literature review, and revised the entire manuscript.

D. Haines supervised the development and interpretation of the antineutrophil antibody assays for each of the patients, assisted with interpretation of the laboratory data, and revised the manuscript specific to the laboratory diagnostics.

Book Review
Compte rendu de livre

Animal Welfare: Global Issues, Trends and Challenges. Scientific and Technical Review, Vol. 24 (2)

Various authors, World Organization for Animal Health (OIE), Paris, France, 2005. 813 pp. ISBN 9-2904-4657-9.

In 2002, the World Organization for Animal Health (OIE) expanded its mandate to become the leading international body in the field of animal welfare, after a unanimous decision from its 167 member countries. It is in this context that the OIE has published a special issue of the Scientific and Technical Review, containing a compilation of papers dealing with Animal welfare: global issues, trends, and challenges. The publication is divided into 5 sections and a conclusion paper.

The 1st section deals with the science-based evaluation of animal welfare including farm, companion, laboratory, wild, captive, and aquatic animals. An attempt at defining animal welfare is made in this section and at determining whether it is a scientific discipline. The term does not express a scientific concept but, because the scientific method is used to identify, interpret, and implement societal concerns about animal quality of life issues, animal welfare has evolved to become a scientific field. Although a precise scientific definition of animal welfare is impossible, a broad working description of welfare is suggested, which includes the notions of the animal in complete mental and physical health, the animal in harmony with its environment, the animal being able to adapt, without suffering, to an artificial environment provided by human beings and, somehow, the animal's feelings should be taken into account. Indirect methods can be used to "ask" the animals what they feel about the conditions they are kept under and the procedures they are subjected to.

The paper dealing with companion animals addresses the concept that the way in which humans treat animals is based on their views of themselves, as well as the living environment around them, and there is a wide range of assumptions that apply to these views. There is an increasing body of evidence