CASE REPORT

Monoclonal gammopathy without hyperglobulinemia in 2 dogs with IgA secretory neoplasms

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Abstract: Two dogs, an 8.5-year-old intact male Golden Retriever and a 10-year-old spayed female English Springer Spaniel, each with varied clinical histories, were referred to the Colorado State University Veterinary Teaching Hospital for evaluation of hypercalcemia and severe anemia, respectively. In each dog, serum total protein and globulin concentrations were within reference intervals. Cytologic examination of bone marrow aspirates from both dogs revealed moderate to marked numbers of atypical lymphoid cells with plasma cell features. Using serum immunofixation and serum immunoglobulin (Ig) quantification, a monoclonal Ig protein was identified. In conjunction with other clinicopathologic and molecular findings, IgA secretory neoplasms, B-cell lymphoma with plasmacytoid features and multiple myeloma (MM), were diagnosed. To our knowledge, these cases represent the first descriptions of IgA-secreting neoplasms in dogs that lacked hyperglobulinemia. In cases of suspected B-cell lymphoma or MM in dogs, serum proteins should be fully evaluated for the presence of a monoclonal Ig even in dogs that lack characteristic hyperproteinemia or hyperglobulinemia. This evaluation will aid in the diagnosis of secretory B-cell lymphoma or MM leading to appropriate clinical and therapeutic case management.

Case Presentations

Dog 1

An 8.5-year-old intact male Golden Retriever of 27.5 kg was presented to the internal medicine service at the Colorado State University Veterinary Teaching Hospital (CSU-VTH) for evaluation of anorexia, lethargy, polyuria, polydipsia, hypercalcemia, and thrombocytopenia. Detailed history revealed that the dog had become increasingly lethargic, polyuric, and polydipsic over the previous 2 weeks and anorectic 3 days before presentation. On presentation, the dog was quiet and no abnormalities were detected on physical examination. Blood collected in tubes containing EDTA and in plain tubes was submitted to the CSU-Clinical Pathology Department for a CBC (Bayer Advia 120 analyzer, Seimens Corporation, New York, NY, USA), serum biochemical profile (Hitachi 911, Roche-Boehringer Mannheim, Indianapolis, IN, USA), and measurement of ionized calcium concentration (ABL 805, Radiometer America, Copenhagen Denmark). Urine was submitted for urinalysis.

CBC abnormalities included moderate thrombocytopenia (73,000/µL, reference interval [RI] 200,000–500,000/µL) with occasional platelet clumps and giant platelets seen on the blood smear, moderately increased mean platelet volume (24.8 fL, RI 7.5–14.6 fL), and mild metarubricytosis characterized by 1 nucleated RBC (nRBC). Platelet clumping may have affected validity of the platelet count, but the interpretation of moderate thrombocytopenia was supported by smear review. Furthermore, identification of giant platelets and increased mean platelet volume suggested increased thrombopoiesis.¹ The most significant biochemical result was severe hypercalcemia (18.3 mg/dL, RI 9.2–11.7 mg/dL), which was confirmed by an ionized calcium concentration of 2.2 mmol/L (RI 1.2–1.5 mmol/L). Other abnormalities included mild azotemia, characterized by increased urea (47 mg/dL, RI 7–32 mg/dL) and creatinine (1.6 mg/dL, RI 0.4–1.5 mg/dL) concentrations, mild
hypomagnesemia (1.8 mg/dL, RI 1.9–2.7 mg/dL), and mildly increased total CO₂ concentration (28 mmol/L, RI 16–25 mmol/L). Total protein (7.0 g/dL, RI 5.3–7.2 g/dL) and globulin (3.1 g/dL, RI 2.0–3.8 g/dL) concentrations were within reference intervals. Urinalysis performed on urine obtained by cystocentesis demonstrated iso-sthenuria (specific gravity 1.008) with rare RBC, WBC, and granular casts. Proteinuria was not detected using a standard reagent strip (Multistix, Bayer Corp., Elkhart, IN, USA) or with sulfosalicylic acid precipitation. The dog was admitted to CSU-VTH and intravenous 0.9% NaCl was administered overnight. The following morning the ionized calcium concentration was unchanged. Parathyroid hormone-related peptide (PTHrP) concentration in plasma sent to the Michigan State University Diagnostic Center was 0 pmol/L (RI, 0–1.0 pmol/L).

Cytologic evaluation of a bone marrow aspirate collected from the proximal aspect of the right femur revealed highly cellular spicules with orderly maturation of erythroid and myeloid cells. In addition, atypical large mononuclear cells accounted for 43% of all nucleated cells (Figure 1A). These cells exhibited large nuclei that were ovoid to round to irregularly shaped with finely stippled chromatin and variable numbers of large nucleoli. The cells had scant to moderate amounts of deeply basophilic cytoplasm. Occasional cells displayed prominent paranuclear clear zones, eccentrically located nuclei with condensed chromatin, or bi- and trinucleation, with marked anisokaryosis and anisocytosis. Based upon cytomorphologic features, the neoplastic cells were tentatively identified as lymphocytes with plasmacytoid features and the presumptive diagnosis was B-cell lymphoma. Determination of immunophenotype by flow cytometric analysis or PCR for antigen receptor rearrangement (PARR) was recommended. Fine-needle aspirates of the popliteal lymph nodes were nondiagnostic, containing only mature adipocytes and blood. Based on the plasmacytoid features of the atypical cells, multiple myeloma (MM) was also a differential diagnosis, and survey skeletal radiographs and evaluation of serum for monoclonal gammopathy were also recommended.

Skeletal survey radiographs and flow cytometric analysis were not performed, but consent was given for PARR and evaluation of serum for a monoclonal gammopathy. Serum was submitted for immunoglobulin (Ig) quantification and immunofixation electrophoresis. Ig quantification (Kent Laboratories, Bellingham, WA, USA) revealed a marked increase in IgA concentration (1035 mg/dL, RI 40–60 mg/dL) concurrent with moderately decreased concentrations of IgG (414 mg/dL, RI 1000–2000 mg/dL) and IgM (40 mg/dL, RI 100–200 mg/dL). Immunofixation electrophoresis (HYDRASYS Agarose Gel Electrophoresis System, Sebia Inc., Norcross, GA, USA; anti-lg antibodies, Bethyl Laboratories Inc., Montgomery, TX, USA) revealed a dense and discrete single band within the IgA lane, indicative of an IgA monoclonal protein (M-protein) (Figure 1B). The PARR assay was performed at CSU on both blood and bone marrow in order to increase the likelihood of detecting neoplastic cells. Analysis revealed a clonal B-cell population in both blood and bone marrow (Figure 1C) even though abnormal lymphocytes were not detected in the CBC. Based upon these findings, the final diagnosis was
secretory IgA B-cell lymphoma, although MM was considered a possibility.

The dog was initially treated with intravenous dexamethasone sodium phosphate (0.2 mg/kg), subcutaneous L-asparaginase (10,000 IU/m^2), and oral prednisone (2.0 mg/kg SID × 7 days) followed by a chemotherapeutic protocol incorporating cyclophosphamide (240 mg/m^2), vincristine (0.7 mg/m^2), and doxorubicin (30 mg/m^2). Two weeks after initiation of therapy, total calcium, ionized calcium, and creatinine concentrations were within reference intervals and the urea concentration (33 mg/dL) was slightly increased. The dog was considered to be in clinical remission, characterized by normalization of clinical signs and serum calcium concentration (10.3 mg/dL), and remained in remission until 32 weeks after initial presentation when the dog was presented to the CSU-VTH for worsening lethargy.

Dog 2

A 10-year-old spayed female English Springer Spaniel was referred to the Oncology Service at CSU-VTH for evaluation of a nasal adenocarcinoma diagnosed 3 months previously by histopathologic evaluation, epistaxis, and severe anemia. On presentation, the dog was quiet and alert with normal body temperature and heart rate. Physical examination revealed increased respiratory stridor and slight serosanguineous discharge from the left nostril. There was no evidence of metastasis on thoracic radiographs. Blood in EDTA and plain tubes and urine were submitted to the CSU Clinical Pathology Laboratory for a CBC, serum biochemical profile, and urinalysis.

CBC results included leukopenia (WBC count 2.0 × 10^3 cells/µL, RI 4.5–15.0 × 10^3 cells/µL) with neutropenia (1.3 × 10^3 cells/µL, RI 2.6–11.0 × 10^3 cells/µL) and lymphopenia (0.3 × 10^3 cells/µL, RI 1.0–4.8 × 10^3 cells/µL); severe nonregenerative anemia with decreased HCT (12%, RI 40–55%), RBC count (1.6 × 10^6 cells/µL, RI 5.5–8.5 × 10^6 cells/µL), and hemoglobin concentration (3.8 g/dL, RI 13.0–20.0 g/dL), normal reticulocyte concentration (9720 cells/µL), and decreased total CO2 (15 mmol/L) concentrations were identified. CBC revealed leucopenia (WBC count 4.3 × 10^3 cells/µL, RI 4.5–15.0 × 10^3 cells/µL) with lymphopenia (0.9 × 10^3 cells/µL, RI 1.0–4.8 × 10^3 cells/µL); nonregenerative anemia with decreased HCT (31%, RI 40–55%), RBC count (4.8 × 10^6 cells/µL, RI 5.5–8.5 × 10^6 cells/µL), and hemoglobin concentration (10.9 g/dL, RI 13.0–20.0 g/dL), and a normal reticulocyte concentration (24,000 cells/µL, RI 0–60,000 cells/µL). Cytologic evaluation of fine-needle aspirates of the liver identified a population of atypical large mononuclear cells identical to those observed in the previously evaluated bone marrow sample. Bone marrow evaluation and IgA quantification were not performed. At this time, chemotherapy was reinitiated (subcutaneous L-asparaginase [10,000 IU/m^2], oral prednisone [2.0 mg/kg SID × 7 days], cyclophosphamide [240 mg/m^2], vincristine [0.7 mg/m^2], and doxorubicin [30 mg/m^2]). Nine days after the reinstitution of treatment, the calcium (9.8 mg/dL) and globulin (2.4 g/dL) concentrations normalized and currently, 21 months after the original diagnosis, the dog is in remission.

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Owing to pancytopenia detected on the CBC, a bone marrow aspirate was collected from the proximal aspect of the left femur. Cytologic evaluation revealed highly cellular spicules with few erythroid and myeloid cells. Greater than 95% of all nucleated cells were intermediate-sized plasma cells with moderate to abundant, often glassy cytoplasm and round, eccentrically located nuclei with coarse chromatin. Skeletal survey radiographs revealed numerous punctate luencies in multiple long bones (diaphyses of bilateral humeri, radii, ulnas, femurs, and tibiae) and vertebrae. Ultrasonographic evaluation of the abdomen revealed mild hepatomegaly with several hyperechoic nodules, hyperechoic renal cortices with mildly reduced
corticomedullary distinction, and an enlarged right medial iliac lymph node with a single, hypoechoic nodule. Based upon these findings, serum was submitted for Ig quantification, which revealed markedly increased IgA concentration (> 5000 mg/dL, RI 40–60 mg/dL), with moderately increased IgG concentration (3485 mg/dL, RI 1000–2000 mg/dL), and moderately decreased IgM concentration (27 mg/dL, RI 100–200 mg/dL). These globulin concentrations yielded a value significantly higher than the globulin concentration calculated as part of the serum biochemical profile. The nature of this discrepancy is uncertain. Owing to the magnitude of increase and other evidence indicative of plasma cell dyscrasia (bone marrow plasmacytosis and multiple lytic bone lesions), the IgA fraction was considered to be likely monoclonal in nature. Neither serum protein electrophoresis nor immunofixation electrophoresis was performed. Moreover, based upon its limited magnitude of increase, the IgG was considered to be polyclonal, although in the absence of confirmatory diagnostic tests a second monoclonal fraction could not be ruled out completely. The final diagnosis was secretory IgA MM.

The dog subsequently received a transfusion of a single unit of packed RBCs and was treated with vincristine (0.7 mg/m2), oral prednisone (2 mg/kg TID × 14 days), and tramadol (5 mg/kg, BID × 3 days). Treatment with melphalan (0.1 mg/kg SID × 10 days, then 0.05 mg/kg SID) was initiated on day 7. Twelve weeks following initiation of treatment, there was resolution of the leukopenia (11.1 × 103 cells/µL), neutropenia (9.5 × 103 cells/µL), and thrombocytopenia (215,000/µL), persistence of the lymphopenia (0.2 × 103 cells/µL), and improvement in RBC measurements, including increases in RBC count (4.8 × 106 cells/µL), hemoglobin concentration (10.3 g/dL), and HCT (31%).

Thirty weeks following diagnosis, the dog was presented to the emergency service at the CSU-VTH for progressive weakness, lethargy, and worsening epistaxis. The dog was euthanized owing to concerns regarding progressive MM and nasal carcinoma. Results of a necropsy confirmed MM in liver, bones, and bone marrow at sites previously denoted as lytic. The final diagnosis of the neoplasm in the nasal cavity was squamous cell carcinoma.

Discussion

In this report we describe 2 cases of canine B-cell neoplasia in which serum globulin concentrations were within the reference interval, but in which circulating monoclonal Igs were present. Serum biochemical profiles had yielded equivocal results, and monoclonal IgA gammopathies were readily detected using either immunofixation or Ig quantification. Typically, a monoclonal protein, or M-protein, is suspected after hyperglobulinemia or hyperproteinemia is detected, and then additional more precise and specific diagnostic tests, including agarose gel, cellulose acetate, or capillary zone protein electrophoresis, immunofixation electrophoresis, and immunoelectrophoresis, can be performed on either serum or urine.2–4 To our knowledge, these cases represent the first complete descriptions of Ig-secreting neoplasms in the dog that were associated with unremarkable globulin concentrations. The incidence of this phenomenon is uncertain as testing for an M-protein is not likely to be performed if protein concentrations are within reference interval.

In the first case, immunofixation electrophoresis was chosen rather than serum protein electrophoresis as a second-line assay for M-protein identification because of its increased sensitivity, which has been extensively documented in the human literature. Most notably, in a study describing the clinical features of 1027 newly diagnosed cases of MM, serum cellulose acetate or agarose gel protein electrophoresis detected an M-protein in only 82% of cases, whereas serum immunofixation electrophoresis was diagnostic in 93%.5 Immunofixation electrophoresis permits more precise differentiation of monoclonal and polyclonal gammopathies, is more sensitive for detection of light-chain disease, and is useful for detecting small amounts of M-protein in the presence of normal background Igs or of polyclonal increases in Igs. In addition to enhanced sensitivity, immunofixation electrophoresis permits more complete characterization of M-proteins, including identification of light-chain-only disease and bi- and triclonal gammopathies, distinctions that cannot be made through the use of agarose gel serum protein electrophoresis.6,7

Evidence of the insensitivity of serum total protein or globulin measurements as indicators of M-proteins is best provided by human studies, including: (1) a report of 534 patients with serum M-proteins in which 59% had serum protein values within the reference interval;8 (2) a study of 98 patients with pure light-chain disease in which serum hyperproteinemia was detected in only 5% of cases and hypoproteinemia was found in more than one-third of patients,9 and (3) a report detailing 156 cases of monoclonal gammopathy in which 31% did not have hyperglobulinemia.10 Although similar studies have yet to be performed in
veterinary medicine, review of published reports, including the 3 largest canine case series, suggests that dogs with secretory B-cell neoplasms or MM that lack hyperglobulinemia may be rare or, alternatively, under-reported. In the largest published case series of 60 dogs with MM and in a report detailing the clinicopathologic features of 18 dogs with monoclonal gammopathy,12 hyperglobulinemia was reported in all dogs. Also, globulin concentrations were increased in all dogs in a report that details the microscopic and immunohistochemical features Ig-producing neoplasms in 32 dogs.13 However, although this is the first report documenting features of IgA-secretory neoplasms in which hyperglobulinemia was absent, there are 3 previously published single case reports that identify dogs with non-IgA MM and normal globulin concentrations, including 2 with pure light-chain disease and 1 with minimally productive IgM-secreting MM.6,14,15 Nevertheless, the incidence of this phenomenon in canine cases remains uncertain, as limitations in the inclusion criteria in the reported studies and failure to evaluate for M-protein when protein or globulin concentrations are within reference intervals, prevent formulation of definitive conclusions regarding incidence.

In the 2 cases presented here, we propose that lack of hyperglobulinemia resulted from either M-protein-associated secondary hypogammaglobulinemia (for dog 1) or the IgA nature of the M-protein (for both dogs). Secondary hypogammaglobulinemia, which is an immunosuppressive phenomenon associated with MM, is reported to occur in about 10% of human MM patients and, in 1 report, is most commonly seen in secretory IgA MM.16–19 The mechanism underlying MM-associated hypogammaglobulinemia is unclear, but recent work suggests that appropriate B-cell maturation and Ig production are impaired by defects and deficits in specific T-cell subsets, notably decreases in CD4⁺, CD45R⁺ naïve T-cells and increases in CD8⁺, CD11b⁺ memory T-cells.20,21 The depression of normal Ig production associated with exuberant M-protein production has been described anecdotally, but not specifically described in dogs with MM.22 Our hypothesis is supported by the Ig quantification data, which indicate massive production of the IgA M-protein and mild to moderate decreases in IgG and IgM in the dog with hypercalcemia. In the second dog, the increase in serum IgG concentration was presumed, based upon the limited magnitude of increase, to be polyclonal in nature. The increase may have been secondary to the previously diagnosed nasal carcinoma or hepatic infiltration by the neoplastic cells. Because neither serum protein electrophoresis nor immunofixation electrophoresis data were available, we cannot rule out the possibility of a second IgG clonal product. The second factor contributing to the apparently unremarkable globulin concentrations may relate to the IgA nature of the M-protein. It is possible that globulin concentrations in these cases simply reflect the proportionally low contribution of the IgA fraction to total globulin concentration. According to the CSU Ig quantification reference intervals, the IgA fraction represents only approximately 3% of the total Ig component in the normal dog; therefore, even massive IgA increases seen in these cases were unlikely to be sufficient to increase the overall globulin concentration outside the reference interval.

In the first case, a diagnosis of MM was strongly considered. However, as skeletal radiographic surveys were not performed and bony lysis could not, therefore, be documented, based on the morphologic atypia of the cells infiltrating the bone marrow, which was not typical of plasma cells, a diagnosis of B-cell lymphoma was favored. In our second case, a diagnosis of MM was made through fulfillment of 2–3 required diagnostic criteria, including atypical plasma cells in bone marrow, lytic bone lesions, and probable monoclonal gammopathy. As neither serum protein electrophoresis nor immunofixation electrophoresis data were available in this case, a conclusion of M-protein monoclonality was largely based on the magnitude of the increase in serum IgA concentration, which was > 80 times the upper end of the reference interval. Although extrapolation of monoclonality from a fold increase in a particular Ig class may be imprecise, support for such an interpretation is provided by work in dogs with nonlymphomatous diseases, including atopy, endo- and ecto-parasitism, steroid responsive meningitis–arthritis, and *Ehrlichia canis* infection, in which increases in IgA concentration do not approach the magnitude observed in this case.23–25

Additionally, in each of these cases abnormalities identified on both the CBC and serum biochemical profile included changes typical of canine MM, such as thrombocytopenia (2/2) and hypercalcemia (1/2). Thrombocytopenia is reported in approximately one-third of all canine cases of MM and is proposed to result from infiltration of bone marrow by malignant plasma cells, consumption of platelets as part of a thrombocytic syndrome, such as DIC, shortened platelet half-life, or immune-mediated destruction, although the latter 2 have yet to be verified in veterinary medicine.11,22,26–28 Hypercalcemia is reported in 15–20% of cases of canine MM and is proposed to result from tumor-mediated osteolysis, tumor production of PTHrP, or an increase in M-protein bound...
calcium.\textsuperscript{11,22,29–31} Finally, although to our knowledge a particular immunophenotype has yet to be determined for canine MM, further confirmation of the plasma cell lineage in these cases may have been aided by immunostaining using the Mum-1p antibody, which has recently been validated in canine formalin-fixed, paraffin-embedded tissues.\textsuperscript{32} This immuno-
staining was not performed in either of the 2 cases presented here.

In this report, we emphasize that monoclonal gam-
mopathy cannot be ruled out on the basis of unremark-
able serum total protein and globulin concentrations. Thus, we propose that adjunctive protein diagnostic tests, including immunofixation electrophoresis and Ig quantification, be included in the standard workup of cases of suspected secretory B-cell neoplasia, regardless of total protein and globulin concentrations. This evaluation will aid in the diagnosis of secretory B-cell lymphoma and MM leading to appropriate clinical and therapeutic case management.

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