Monoclonal immunoglobulin protein production in two dogs with secretory B-cell lymphoma with Mott cell differentiation

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Case Description—A 9-year-old castrated male mixed-breed dog and a 7-year-old spayed female Boston Terrier, with clinical histories of a liver mass (dog 1) and bloody vomitus, diarrhea, and weight loss (dog 2), respectively, were referred for further evaluation.

Clinical Findings—At the time of referral, each dog had differing laboratory abnormalities; however, the serum total protein and globulin concentrations were within reference range in both dogs. Cytologic examination of fine-needle aspirates obtained from affected organs (a liver mass [dog 1] and enlarged submandibular lymph node [dog 2]) revealed 2 main nucleated cell types: atypical lymphoid cells and lesser numbers of Mott cells. With the use of serum immunofixation electrophoresis and serum immunoglobulin quantification, a monoclonal immunoglobulin protein was identified in both dogs and a final diagnosis of secretory B-cell lymphoma with Mott cell differentiation (MCL) was made.

Treatment and Outcome—Both dogs received chemotherapy for their disease. The first dog was euthanized 8.5 months after diagnosis because of acute respiratory distress of unknown etiology, and the second was euthanized 7 days after diagnosis for worsening clinical disease and quality of life.

Clinical Relevance—To our knowledge, this report is the first of a secretory form of MCL in dogs. Findings indicate that in dogs with suspect MCL, even in patients that lack characteristic hyperproteinemia or hyperglobulinemia, serum protein content should be fully evaluated for the presence of a monoclonal immunoglobulin protein. Such an evaluation that uses immunofixation electrophoresis and immunoglobulin quantification will aid in the diagnosis of MCL in dogs. (J Am Vet Med Assoc 2011;239:1477–1482)

A 28-kg (62-lb) 9-year-old castrated male mixed-breed dog (dog 1) was referred to the Oncology Service at the Colorado State University Veterinary Medical Center for further evaluation of a liver mass and peritoneal effusion. The mass was identified 7 days earlier by the referring veterinarian, and at that time, cytologic examination of an aspirate revealed a round cell tumor of uncertain cytogenensis. Further anamnesis revealed that the dog had clinical signs of increasing lethargy, depression, difficulty defecating, and progressive abdominal distension of 2 weeks' duration. At the time of admission, the dog was bright and alert with a body temperature, heart rate, and respiratory rate within reference range. Physical examination revealed marked abdominal distension with palpable organomegaly in the cranial portion of the abdomen. No other physical examination abnormalities were appreciated. Samples of peritoneal fluid were obtained for cytologic analysis, and serum samples were submitted for SPE, IFE, and IgQ. Additionally, fine-needle aspirates of the liver mass were submitted for cytologic examination and PARR, and needle biopsy specimens of the mass were submitted for histologic evaluation.

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Abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>IFE</td>
<td>Immunofixation electrophoresis</td>
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<td>IgQ</td>
<td>Immunoglobulin quantification</td>
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<tr>
<td>MCL</td>
<td>B-cell lymphoma with Mott cell differentiation</td>
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<tr>
<td>M protein</td>
<td>Monoclonal immunoglobulin protein</td>
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<td>PARR</td>
<td>PCR assay for antigen receptor rearrangement</td>
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<td>SPE</td>
<td>Serum protein electrophoresis</td>
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Results of a CBC, serum biochemical analysis, and urinalysis obtained 7 days prior to admission to the Colorado State University Veterinary Medical Center revealed only a minimal decrease in mean cell hemoglobin concentration (29.3 g/dL; reference range, 30 to 37.5 g/dL) and a mild hyperbilirubinemia (1.1 mg/dL; reference range, 0 to 0.9 mg/dL). The urinalysis performed on a urine sample obtained from the urinary bladder by use of a urethral catheter revealed adequate urine-concentrating ability (specific gravity > 1.050), and testing with a standard urine reagent dipstick revealed a high end of reference range value for urine protein concentration (30 mg/dL; reference range, 15 to 30 mg/dL) and moderate ketonuria (40 mg/dL; reference range, < 5 to 10 mg/dL). At this time, the serum total protein (7.0 g/dL; reference range, 5.2 to 8.2 g/dL), albumin (3.3 g/dL; reference range, 2.2 to 3.2 g/dL), and globin concentration (29.3 g/dL; reference range, 30 to 40 g/dL) were within reference ranges. A dipstick revealed a high end of reference range value for urine protein concentration (30 mg/dL; reference range, 15 to 30 mg/dL) and moderate ketonuria (40 mg/dL; reference range, < 5 to 10 mg/dL). At this time, the serum total protein (7.0 g/dL; reference range, 5.2 to 8.2 g/dL), albumin (3.3 g/dL; reference range, 2.2 to 3.2 g/dL), and globin concentration (29.3 g/dL; reference range, 30 to 40 g/dL) were within reference ranges.
to 3.9 g/dL), and globulin (3.7 g/dL; reference range, 2.5 to 4.5 g/dL) concentrations were within reference range. Abdominal ultrasonography performed by the referring veterinarian revealed a single large mass involving the left medial and caudate liver lobes of the liver as well as heterogeneous nodular masses throughout the remaining hepatic parenchyma, a moderately enlarged spleen, and a moderate amount of free peritoneal fluid.

Analysis of a peritoneal fluid sample revealed a red, opaque fluid with a yellow, clear supernatant that contained 7,730 nucleated cells/µL, 1.3 × 10⁶ RBCs/µL, a PCV of 8%, and a total protein concentration as determined by refractometry of 4.3 g/dL. On cytologic examination, the peritoneal fluid had a mixture of neutrophils, macrophages, and fewer lymphocytes with rare macrophages undergoing erythrophagocytosis; these findings were interpreted as mild, mixed inflammation with previous hemorrhage.

Cytologic examination of fine-needle aspirates from the liver mass revealed highly cellular samples with a small amount of blood contamination (Figure 1). Dispersed throughout the slides was a pale blue, homogenous, and proteinaceous background that contained a mixture of many broken cells and scattered round, variably sized globules that were either clear or pale blue, consistent with lipid and free Russell bodies, respectively. Two main nucleated cell populations were identified: 63% of an intermediate- to large-sized population of lymphoid cells and 14% large cells with myriad, intracytoplasmic vacuoles (Mott cells). The intermediate- to large-sized lymphoid cells were round, 12 to 24 µm in diameter, and characterized by moderate to marked anisocytosis and anisokaryosis. These cells had a small amount of moderately blue cytoplasm, a high nuclear-to-cytoplasmic ratio, and round to oval nuclei with smooth chromatin. The Mott cells were round, 25 to 35 µm in diameter, and characterized by moderate anisocytosis and anisokaryosis. Mott cells had eccentrically positioned round to oval nuclei containing smooth chromatin and, within their cytoplasm, a variable number of differently sized, round, clear to pale blue bodies (Russell bodies). Based on the cytomorphologic similarities between these cells and those described in previous reports, the B-cell phenotype was consistent with a primary differential diagnosis of MCL.

Results of the SPE revealed a single spike within the α, region, which was interpreted to be the result of increased acute-phase proteins, and a broad, low peak within the globulin region, which was interpreted to be a normal finding (Figure 1). No evidence of a monoclonal gammapathy was described. Findings on IFE of sera revealed a single, distinct band within the IgA lane, which was interpreted as evidence of a neoplastic serum M protein. The presence of the M-protein was determined by use of IgQ, which revealed a marked increase in serum IgA concentration (1,607 mg/dL; reference range, 40 to 60 mg/dL) with mildly low serum IgG (858 mg/dL; reference range, 1,000 to 2,000 mg/dL) and IgM (94 mg/dL; reference range, 100 to 200 mg/dL) concentrations. Results of PARR revealed a clonal B-cell population in the peritoneal effusion through the demonstration of a clonal immunoglobulin gene rearrangement. Flow cytometric analysis of a liver aspirate revealed that 95% of the large cells expressed CD21 and CD22 (B-cell antigens). On the basis of these findings, a final diagnosis of normoglobulinemic, IgA secretory, hepatic MCL was made.

Histologic examination of the liver needle biopsy specimens revealed tissue sections devoid of typical hepatic constituents and consisting entirely of sheets of round to oval cells containing minimal amounts of blue cytoplasm and moderate numbers of Mott cells. Immunohistochemical staining of samples from the hepatic mass with antisera specific to canine IgA, IgG, IgM heavy chain, and κ and λ immunoglobulin light chains was performed at the University of Minnesota’s Veterinary Diagnostic Laboratory. Results indicated that neoplastic cells expressed the IgA heavy chain with a small number of nonneoplastic lymphocytes and plasma cells having IgG heavy-chain expression. Moreover, most neoplastic cells expressed the λ light chain with no anti-κ light-chain immunoreactivity detected (data not shown). There was insufficient tissue remaining to evaluate for other B-cell markers, including CD79a and Pax-5.

**Figure 1**—Photomicrograph of a fine-needle aspirate of a liver mass (A) and results of SPE (B) and serum IFE (C) of a 9-year-old castrated male mixed-breed dog (dog 1) evaluated because of a hepatic mass. **A**—On cytologic evaluation of the liver mass, notice the 2 nucleated cell populations: intermediate-sized to large lymphoblasts (arrowhead) and large cells with myriad, intracytoplasmic vacuoles (Mott cells). The intermediate- to large-sized lymphoid cells were round, 12 to 24 µm in diameter, and characterized by moderate to marked anisocytosis and anisokaryosis. **B**—In the SPE tracing, notice the single, discrete and narrow peaks within the α and β regions that indicate increased acute-phase proteins. **C**—In the IFE gel, notice a single restricted M-protein band that is identified within the α (IgA) well. The remaining wells are devoid of appreciable bands (L, light chain and M, IgM) or contain a broad smear (IgG). G indicative of a polyclonal immunoglobulin population. A = Anti-dog IgA (heavy chain). Alb = Albumin. G = Anti-dog IgG (heavy and light chains). L = Anti-dog λ and κ light chains. M = Anti-dog IgM (heavy chain). WS = Whole serum.
Following the provision of the final diagnosis, a standard chemotherapeutic treatment regime (ie, CHOP) of cyclophosphamide (250 mg/m², PO), vincristine (0.5 mg/m², IV), doxorubicin (30 mg/m², IV), and prednisone (1.8 mg/kg [0.8 mg/lb], PO, q 24 h for 7 days, then tapered by 25% over 24 days) was instituted. The patient was assessed weekly for a clinical remission throughout the protocol. Abdominal ultrasonography was repeated after the first cycle of chemotherapy (week 6) as well as at the completion of the 19-week protocol; both ultrasonographic examinations revealed complete remission. On the basis of the lack of ultrasonographic abnormalities, fine-needle aspirates were not obtained.

Four weeks after completing the 19-week cyclophosphamide, doxorubicin, vincristine, and prednisone protocol at the Colorado State University Veterinary Medical Center, the dog was admitted to the Colorado State University Veterinary Medical Center Oncology Service for vomiting and lethargy. Abdominal ultrasonography revealed a 2.1 × 3.1-cm mass in the left lateral liver lobe. There were multiple hypoechoic nodules in the splenic parenchyma, with the largest of these nodules measuring 2.7 × 3.0 cm. Fine-needle aspirates were obtained from the spleen, revealing recurrence of disease. On the basis of these findings, the dog was started on a lomustine and 1-asparaginase rescue protocol (lomustine, 70 mg/m², PO, q 3 wk with 1-asparaginase, 10,000 U, administered SC at the first and second doses of lomustine). The dog continued to receive lomustine every 3 to 4 weeks for a total of 4 treatments until it was euthanized for acute respiratory distress of unknown etiology 255 days after beginning initial treatment. A necropsy was not performed.

A 7-kg (15.4-lb) 7-year-old spayed female Boston Terrier (dog 2) was evaluated by a referring veterinarian because of a 1-week history of bloody vomitus, diarrhea, and weight loss. At the time of initial evaluation by the referring veterinarian, the dog was bright and alert with a body temperature, heart rate, and respiratory rate within reference range. Physical examination revealed peripheral lymphadenomegaly with bilateral enlargement of the submandibular, prescapular, and popliteal lymph nodes. No other abnormalities were appreciated on physical examination. Whole blood and serum samples were submitted to a commercial veterinary diagnostic laboratory for a CBC and serum biochemical analysis, and fine-needle aspirates of the left submandibular lymph node were collected for cytologic examination.

Results of the CBC determined by use of an analyzer revealed a mild anemia characterized by mild decreases in Hct (30%; reference range, 36% to 60%), RBC count (4.1 × 10¹² cells/µL; reference range, 4.8 × 10¹² cells/µL to 9.3 × 10¹² cells/µL), and hemoglobin concentration (9.4 g/dL; reference range, 12.1 to 20.3 g/dL). The platelet count was mildly decreased (128,000 cells/µL; reference range, 170,000 to 400,000 cells/µL), although evaluation of the blood smear revealed platelet clumps. Additionally, a mild metarubricytosis was seen (7 nucleated RBCs/100 WBCs; reference range, 0 to 1 nucleated RBCs/100 WBCs). The serum biochemical analysis determined by use of a chemistry analyzer revealed a mild hypoproteinemia characterized by mild decreases in total protein (3.7 g/dL; reference range, 5.0 to 7.4 g/dL) and albumin (1.6 g/dL; reference range, 2.7 to 4.4 g/dL) concentrations and a globulin concentration within reference range (2.1 g/dL; reference range, 1.6 to 3.6 g/dL). Additionally, a mild decrease in calcium concentration (7.5 mg/dL; reference range, 8.9 to 11.4 mg/dL) was observed.

Cytologic examination of fine-needle aspirates from the left submandibular lymph node revealed highly cellular samples in which a heterogenous population of lymphoid cells was dispersed throughout a blue, homogenous, and proteinaceous background containing many broken cells. Of the intact nucleated cells, 4 main populations were identified: morphologically normal, small lymphocytes (31% of cells); normal-appearing prolymphocytes (29%); large atypical lymphoid cells (17%); and somewhat atypical Mott cells (23%). The large atypical lymphoid cells were round to oval and contained a modest amount of pale blue cytoplasm with round nuclei containing coarse and clumped chromatin. A modest number of these cells contained few to myriad, discrete, round, and clear intracytoplasmic vacuoles (Figure 2). The Mott

![Figure 2](https://example.com/image2.png)
cells contained a round to oval, somewhat eccentrically positioned nucleus with smooth to finely granular chromatin and variable numbers of round, clear to pale blue bodies. Within this population, there was moderate atypia characterized by scattered cells with large nuclei or coalescing Russell bodies. In the background, there were many broken cells and numerous, variably sized globules, consistent with either lipid or free Russell bodies.

These cells were interpreted to be lymphoid in origin, and on the basis of the cytomorphologic similarities between these cells and those described in previous reports, a diagnosis of MCL was proposed, although a reactive process was considered as a lesser differential diagnosis. To aid in distinguishing between these 2 diagnoses, flow cytometry and PARR testing of aspirates as well as histologic examination of a submandibular lymph node biopsy specimen were recommended. Additionally, because of the potential secretory nature of possible B-cell neoplasm, it was recommended that sera be submitted for SPE, IFE, and IgQ to test for the presence of an M protein. Following receipt of these recommendations, the dog was referred to a second clinic (Pet Emergency and Specialty Center, La Mesa, Calif), where abdominal ultrasonography was performed and treatment for presumed B-cell lymphoma was instituted.

Abdominal ultrasonography revealed enlarged gastric, hepatic, and sublumbar lymph nodes, moderate gastric wall thickening, and a mildly hypoechogenic and enlarged pancreas. Results of the SPE (Figure 2) revealed a series of peaks within the α2 region, the tallest of which was characterized by a discrete, narrow apex. These findings were interpreted as a probable increase in acute-phase proteins, although the presence of an M protein could not be excluded. Findings on IFE of a serum sample revealed a single, distinct band within the IgM lane and a similarly discrete and corresponding band within the light-chain lane, findings that were interpreted to be indicative of an IgM M protein. Findings on IgQ revealed a moderate increase in serum IgM concentration (682 mg/dL; reference range, 100 to 200 mg/dL) with a mildly low serum IgG (776 mg/dL; reference range, 1,000 to 2,000 mg/dL) concentration and a serum IgA concentration within reference range (85 mg/dL; reference range, 40 to 160 mg/dL). Findings on PARR did not identify a clonal lymphoid population. On the basis of these findings, a final diagnosis of normoglobulinemic, IgM, secretory MCL was made.

The dog was initially treated for MCL with l-asparaginase (80,000 U/m2, SC) and oral administration of prednisone (0.9 mg/kg [0.4 mg/lb], q 12 h). One day following the initiation of chemotherapy, the dog was brought to the referral clinic because of anorexia, decreased thirst, and severe lethargy, vomiting, and diarrhea. At that time, physical examination revealed mildly enlarged prescapular and submandibular lymph nodes, which were interpreted to be decreased in size since the onset of treatment. The owner declined hospitalization, and the dog was treated with doxorubicin (25 mg/m2, IV), ondansetron (0.5 mg/kg [0.2 mg/lb], SC, q 12 h), diphenhydramine (1.9 mg/kg [0.84 mg/lb], IV, q 24 h), and a polyionic electrolyte solution (200 mL, SC, q 24 h). The following day, the dog was evaluated for worsening lethargy, diarrhea, and vomiting. A repeated CBC was performed and revealed a moderate nonregenerative anemia (blood smear evaluation revealed minimal polychromasia) characterized by a decrease in Hct (16.2%; reference range, 37% to 55%), RBC count (2.55 × 106 cells/µL; reference range, 4.8 × 106 cells/µL to 9.3 × 106 cells/µL), and hemoglobin (5.8 g/dL; reference range, 12 to 18 g/dL) concentrations. Additionally, a marked lymphopenia (0.2 × 109 cells/µL; reference range, 1.2 × 109 cells/µL to 5.0 × 109 cells/µL) and a moderate thrombocytopenia (86,000 cells/µL; reference range, 200,000 to 500,000/µL) were detected. Because of concerns regarding hemorrhage from the gastrointestinal tract, the dog was treated with maropitant citrate (1.1 mg/kg [0.5 mg/lb], SC, q 24 h), sucralfate (0.5 g, PO, q 8 h), and famotidine (0.7 mg/kg [0.3 mg/lb], PO, q 12 h). The owner again declined hospitalization, and 4 days later, 7 days after the initiation of chemotherapy, the dog was euthanized because of worsening of clinical signs. A necropsy was not performed.

**Discussion**

Lymphoma is a relatively common tumor in dogs, representing approximately 7% to 24% of neoplasms and 83% percent of all hematopoietic neoplasms. Although most cases of lymphoma in dogs (70% to 80%) are of a B-cell phenotype, MCL is an uncommon variant, having previously been described in only 3 reports, totaling 4 dogs. B-cell lymphoma with Mott cell differentiation in dogs has been described as a cytomorphologically unique form of gastrointestinal lymphoma with primary disease arising in the stomach or small intestine and lacking neoplastic M-protein production in serum. In affected dogs, monoclonal immunoglobulin gene rearrangements, flow cytometric features consistent with a B-cell–origin tumor, and findings on electron microscopy of 2 populations of round cells (ie, intermediate- to large-sized lymphocytes and Mott cells with endoplasmic reticulum containing immunoglobulin) have been described. Findings for the dogs of the present report differ from those reported previously in that these 2 dogs had evidence of M-protein secretion by the neoplastic B cells. Findings in the dogs of the present report emphasize the following: cytomorphic examination of fine-needle aspirates obtained from affected organs is useful in the diagnosis of MCL; dogs with MCL can have an increase in M-protein production but still have serum total protein or globulin concentrations within reference range or have unremarkable SPE results; and the detection of neoplastic M-protein production, by providing surrogate evidence of a neoplastic cell population, can facilitate the diagnosis of MCL in dogs.

For the 2 dogs of the present report, a diagnosis of MCL was initially favored solely on the basis of the cytologic features of fine-needle aspirates, which revealed a biphasic population of lymphoid cells: atypical, small to medium-sized lymphocytes and Mott cells. These findings confirm the usefulness of cytology as a primary diagnostic tool and concur with previously published descriptions of MCL in dogs, which describe 2 similarly distinct and variably proportioned popula-
tions of atypical cells.\cite{1,3} Although aspirational cytologic evaluation provided the initial evidence for MCL, an ultimate diagnosis of B-cell lymphoma was confirmed through the identification of a clonal B-cell population. The presence of such a clonal population was demonstrated by the detection of an M protein in sera (dogs 1 and 2) with or without positive PARR results (dog 1). The use of PARR was valuable in the diagnostic workup of these 2 dogs. Although the positive PARR result of dog 1 is consistent with findings of dogs in a previous report,\cite{7} in which 3 of 3 dogs with MCL had a positive PARR result, the negative PARR result for dog 2 was surprising. We propose that this negative PARR result in dog 2 may represent a false negative, which is reported to occur for 9% of dogs with lymphoma.\cite{8}

Despite the fact that serum total protein and globulin concentrations were within reference range for each of the 2 dogs of the present report, a recent report\cite{4} of normoglobulinemic, normoproteinemic, secretory B-cell neoplasia in 2 dogs led us to evaluate for the possible presence of an M protein. The M protein is a product produced from a specific B-cell clone and can consist of an entire immunoglobulin molecule, a heavy chain only, or a light chain only (Bence-Jones protein). Suspicion for the presence of an M protein is most commonly provided by high serum total protein and globulin concentrations, although more specific diagnostic testing, including SPE, IFE, and IgQ, are necessary to confirm the monoclonality of the protein product in serum. In dogs, there are a small number of diseases associated with the production of an M protein, including certain infectious diseases (ehrlichiosis and leishmaniosis), rare cases of inflammatory disease (pyoderma and gastroenterocolitis), idiopathic states (so-called idio- pathic paraproteinemia), and, most commonly, immunoglobulin-producing tumors.\cite{5,9} Neoplasms reported to produce detectable M proteins in dogs include B-cell lymphocytic leukemia, B-cell lymphoma, lymphoplas- myctic lymphoma (ie, Waldenström’s macroglobulinemia), mucocutaneous plasmacytoma, and, more commonly, multiple myeloma.\cite{10} To the authors’ knowledge, no reports of M-protein–producing MCL in dogs have been reported.

The identification of an M protein in normopro- teinemic or normogobulinemic patients, although still relatively novel in veterinary medicine, is quite common in human medicine. Such a phenomenon is best exemplified by 2 studies\cite{11,12} one showing that most (99%) humans with secretory multiple myeloma have serum protein concentrations within the reference range and the other demonstrating that 31% of people with multiple myeloma lack hyperglobulinemia. In each of the 2 dogs of the present report, convincing evidence of the presence of an M protein was only demonstrated through the testing of serum by IFE and IgQ, which support the findings in a previous study.\cite{7} These results mirror what has been reported in a series of 1,027 human patients newly diagnosed with multiple myeloma, in which the use of SPE and IFE resulted in the detection of an M protein in sera in 82% and 93% of the patients, respectively.\cite{13} For the 2 dogs of the present report, the use of SPE appeared insensitive for definitive M-protein detection; however, each trac-
in dogs.\textsuperscript{1,2} Unfortunately, adequate tissue samples were not available to pursue additional immunohistochemistry, which would have allowed for comparison with previous reports\textsuperscript{3–5} of MCL in dogs, in which a population of vimentin\textsuperscript{+}, CD20\textsuperscript{+}, CD79a\textsuperscript{+}, Pax-5\textsuperscript{+}, B-lymphocyte antigen 36\textsuperscript{+}, CD45\textsuperscript{+}, CD45RA\textsuperscript{+}, CD3\textsuperscript{+}, and lysozyme \textsuperscript{B} cells has been described.

In addition to MCL, other differential diagnoses considered for each dog included plasma cell neoplasia (ie, malignant plasmacytoma and multiple myeloma) and plasmacytoid T-cell lymphoma. However, the cytomorphologic features of the neoplastic population in these 2 dogs, which did not contain an obvious plasma cell population yet did contain a substantial population of Mott cells, served to rule out these differential diagnoses.\textsuperscript{2,3} Additionally, in dog 1, the atypical, large lymphocyte population was found to express CD21 and CD22, which are not known to be expressed on canine plasma cells.\textsuperscript{2,3}

In this report, a novel feature of MCL in dogs was demonstrated: the capability of detectable M-protein production by the neoplastic cells. Additionally, findings in these 2 dogs with MCL further emphasize that serum total protein or globulin concentrations within reference range or an unremarkable SPE result does not definitively rule out the presence of an M protein. Finally, this report serves to emphasize the greater usefulness of adjunctive protein diagnostic testing, notably testing of sera by IFE and IgQ, over traditional measurement of serum total protein and globulin concentrations in dogs suspected of having an M-protein–producing disease.

References