Multiple myeloma in 16 cats: a retrospective study

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Background: There is limited published information regarding feline multiple myeloma. Diagnostic criteria are derived from canine studies and to our knowledge, have not been critically reviewed for cats. **Objective:** To evaluate the clinical and laboratory findings in cats with multiple myeloma and appraise diagnostic criteria. **Methods:** Retrospective evaluation of medical records was performed. Inclusion required an antemortem diagnosis of multiple myeloma using 2 of 4 criteria: 1) ≥20% plasma cells in the bone marrow, or ≥10% if atypical plasma cells; 2) paraproteinemia; 3) radiographically-evident osteolysis; 4) light chain proteinuria. Alternatively, a postmortem diagnosis was based on the findings of multiple plasma cell neoplasms, with marrow involvement. **Results:** Sixteen cats were diagnosed with multiple myeloma between 1996 and 2004, with a median age of 14.0 years; 9 of 16 (56%) were castrated males, and 7 of 16 (44%) were spayed females. Laboratory abnormalities included hyperglobulinemia (14/16, 87.5%), with 11/14 (78.5%) monoclonal and 3/14 (21.4%) biclonal gammopathies; hypoalbuminemia (4/16, 25%); light chain proteinuria, (4/9, 44.4%); hypocholesterolemia (11/16, 68.7%); hypercalcemia, (3/15, 20%); non-regenerative anemia, (11/16, 68.7%); regenerative anemia, (1/16, 6.2%); neutropenia (5/15, 33.3%); thrombocytopenia (8/16, 50%); and marrow plasmacytosis (14/15, 93.3%). Plasma cells were markedly immature, atypical, or both in 10 of 12 (83.3%) cats. Focal or multifocal osteolysis was noted in 6 of 12 (50%) cats for which radiographs were available for review; generalized osteopenia was found in 1 (8.3%) cat. Noncutaneous, extramedullary tumors were found in all cats assessed, 7/7 (100%), including spleen (6), liver (3), and lymph nodes (4). The disease in 1 of 2 cats with cutaneous tumors progressed to plasmacytic leukemia. **Conclusions:** Common findings in feline multiple myeloma include atypical plasma cell morphology, hypocholesterolemia, anemia, bone lesions, and multi-organ involvement. Based on the results of this study, we advocate modifying diagnostic criteria in cats to include consideration of plasma cell morphology and visceral organ infiltration. (*Vet Clin Pathol.* 2005;34:341–352)
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Multiple myeloma is a multifocal plasma cell neoplasm involving bone marrow. Multiple myeloma patients present with nonspecific and insidious clinical signs such as lethargy, inappetence, weight loss, and intermittent vomiting.[1] It is a rare neoplasm in cats, with an estimated incidence of <1% of all feline hematopoietic neoplasms.[2,3] There are few reports in the literature, with most of these limited to 1 or 2 case studies.[3–14] The largest retrospective report to date was limited to 4 cats.[1] In addition, authors of a review article on causes of monoclonal gammopathy in dogs and cats included limited information regarding 6 cats diagnosed with multiple myeloma over a 6-year period at The Animal Medical Center in New York City.[15] Most information regarding the biology of this disease is derived from human and canine studies. Additional information regarding behavior of the disease in cats and applicability of currently used diagnostic criteria in cats is needed. Therefore, we conducted a retrospective study using biopsy, cytology, and necropsy files from the Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania (MJR-VHUP) School of Veterinary Medicine. We reviewed signalment, clinical features, clinicopathologic findings, and outcome. We compared features seen in cats with multiple myeloma to those historically noted in dogs and people.

Materials and Methods

Cats diagnosed with multiple myeloma from January 1, 1996 to February 1, 2004 were identified via a computer search of biopsy, necropsy, and cytology reports, and coded discharge diagnoses in the MJR-VHUP database. Inclusion in the study required 2 of 4 antemortem criteria: 1) bone marrow plasmacytosis with ≥20% plasma cells, or ≥10% atypical plasma cells; 2) monoclonal or biclonal gammopathy on serum protein electrophoresis (SPE); 3) radiographic evidence of osteolysis; and 4) light chain (Bence-Jones) proteinuria. A plasma cell population was defined as morphologically atypical if >5% of the plasma cells had morphology not associated with normal reactive plasmacytosis, eg, marked anisocytosis, marked anisokaryosis, multinucleation with >2 nuclei, immature chromatin, distinct nucleoli, maturation asynchrony, clefted nuclei, and markedly variable N:C ratios.[16–18] Necropsy diagnoses were based on finding plasma cell tumors with multiple organ and marrow involvement. Incidence of multiple myeloma was calculated by dividing the number of cats with multiple myeloma by the total number of cats with malignancies and by the total number of cats with hematopoietic neoplasms.

Table 1. Clinical signs and physical examination findings in 16 cats with multiple myeloma.

Clinical Sign or Finding	Cat No.	n	%
Listlessness/weakness	1–3, 6, 9–13, 16	10	62.5
Anorexia	1–3, 6, 9–13	9	56.2
Heart murmur	1, 2, 5, 7, 9, 13, 16	7	43.4
Vomiting/diarrhea	1, 3, 7, 10, 12	5	31.2
Pallor	3, 4, 9, 12, 16	5	31.2
Dehydration	2, 6, 9, 10, 16	5	31.2
Orthopedic lameness	8, 11, 14, 16	4	25.0
Palpable cranial abdominal organomegaly	4, 5, 9, 16	4	25.0
Skin masses	5, 8	2	12.5
Lymphadenopathy	7, 9	2	12.5
Recurrent bilateral epistaxis	4	1	6.2
Periodontal disease	2	1	6.2
Retinal hemorrhages	7	1	6.2
Pleural/peritoneal effusions	9	1	6.2
Recurrent upper respiratory infections	10	1	6.2

In bone marrow aspirate smears stained with Wright-Giemsa (Harleco, Gibbstown, NJ) the percentage of plasma cells was determined by assessing 400–500 nucleated cells at the time of the original diagnosis; percentages were rechecked retrospectively by one of the authors (RTP) for the purpose of this study. Histologic preparations were stained with H&E. When histologic sections were used in lieu of aspirates, "plasma cell mass" as a percentage of marrow volume was assessed retrospectively (instead of plasma cell percentage) for this study by one of the authors (AFF).[17]

Complete blood counts were run on an Abbott CELL-DYN 3500 hematology analyzer (Plato, Texas, USA) with multi-species settings. All differential leukocyte counts were determined manually by counting 100 cells and all blood smears also were reviewed by one of the authors (RTP). Routine serum chemistry profiles were analyzed using an Ortho-Clinical Diagnostics VITROS 250 (Rochester, New York, USA). Ionized calcium concentration was determined in some of the cats using a Nova Stat Profile M (Waltham, Massachusetts, USA).

Proteinuria was detected using Bayer Multistix 10SG reagent strips (Elkhart, Indiana, USA) read on a Clinitek 50 urine chemistry analyzer (Bayer). All urine samples were also screened for protein by sulfosalicylic acid (SSA) precipitation. If positive by SSA, urine samples were then tested for light chain proteinuria by either the Bence-Jones heat precipitation method[19] or by immunoelectrophoresis. Light chain proteinuria was determined by the heat precipitation method in 7 cats and by urine protein electrophoresis in 2 cats.

Protein electrophoresis using capillary gel electrophoresis was done on serum from 14 cats (Paragon Electrophoresis System, Beckman Coulter Inc, Ramsey, MN, USA) to evaluate the presence of a monoclonal protein spike (M-protein or M-spike). The stained cellulose acetate strip was scanned with an Appraise clinical densitometer (Beckman). Immunoelectro-

phoresis was done (Helena Laboratories, Beaumont, Texas, USA) using species-specific anti-immunoglobulin (Ig) G, anti-IgM, and anti-IgA to identify the specific type of M-protein in 2 cats. Serum viscosity, relative to water, was determined in 1 cat using a Wells-Brookfield Cone-Plate Viscometer (Oakville, Ontario, Canada), with a ratio >3.5 interpreted as abnormal.[6]

Eight of the 16 cats had feline coronavirus antibody titers determined via serum ELISA (Antech Diagnostics, Lake Success, NY, USA). All cats were tested for feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) using the SNAP combined immunoassay for FeLV antigen and FIV antibody (IDEXX Laboratories, Westbrook, ME, USA).

Results

Historical, clinical, and physical examination findings

Sixteen cats met the diagnostic criteria; 13 were patients at MJR-VHUP and 3 had samples submitted through the external biopsy service. Patient age ranged from 7 to 18 years, with a median of 14 years and mean of 12.6 years. There were 9 castrated males (56%) and 7 spayed females (44%); 13 were domestic shorthair, 2 were domestic longhair, and 1 was a Russian blue cat. The incidence of multiple myeloma at MJR-VHUP during the study period was 0.9% of all cats diagnosed with malignancies (n=1491) and 1.9% of all cats diagnosed with hematopoietic neoplasms (n=670), including lymphoma, during the same period.

Historical and physical examination abnormalities were nonspecific (Table 1), with the exception of 3 cats. Cat 5 had multiple skin masses on the xiphoid, right hock, left flank, cranial thorax, and lumbar back and a gallop cardiac rhythm. Cat 8 had a multilobulated cutaneous tarsal plasma cell tumor diagnosed histologically 6 months previously. Diagnostic evaluation (marrow, serum protein electrophoresis, radiographs) at the time of initial presentation for the tarsal mass was negative for systemic disease or local bone involvement. Cat 10 had an M-protein first detected 9 years earlier. A diagnosis of monoclonal gammopathy of undetermined significance (MGUS) was made based on lack of evidence for multiple myeloma; the cat had no clinical signs, no marrow plasmacytosis, no significant radiographic or ultrasonographic findings, and negative light chain proteinuria.

Clinical pathology data

Relevant laboratory results and bone marrow and extramedullary tissue involvement were summarized (Tables 2–4). Cat 5, with only mild hyperglobulinemia, had hyperviscous serum, based on viscometry. Immunoelectrophoresis for cats 8 and 13 identified the M-protein as IgA and IgG, respectively. Four cats (nos. 2, 7, 9, and 12) were hypoalbuminemic, with albumin values ranging from 1.8–2.3 g/dL (reference interval 2.4–3.8 g/dL).

Protein:creatinine ratios (P:C) were determined in 2 cats with proteinuria. Cat 1 had 2+ proteinuria and a P:C of 0.62 (reference interval 0.5–1.0). Cat 15 had 3+ proteinuria and a P:C of 19.4. Light chain proteinuria, detected by urine protein electrophoresis, was found in both cats tested

Table 2. Selected clinical pathology results at presentation in 16 cats with multiple myeloma.

Cat No.	Serum and Urine			Peripheral Blood				
	Globulins, g/dL	Cholesterol, mg/dL	Urine Protein	HCT, %	WBC, $\times 10^3/\mu L$	Neutrophils, $\times 10^3/\mu L$	Plasma Cells, $\times 10^3/\mu L$	Platelets, $\times 10^3/\mu L$
1	10.0	74	2+	35.2	3.49	2.2	0	256
2	10.5	68	2+	25.2	9.45	7.3	0	248
3	7.3	133	2+	13.6	3.18	2.6	0	98
4	12.5	45	Negative	13.5	5.02	3.2	0	Adequate
5	6.6	82	3+	20.6	20.70	16.0	0	Adequate
6	7.3	63	3+	35.3	5.00	ND*	ND	Decreased
7	10.1	65	Negative	16.2	15.70	11.0	0	Adequate
8	8.4	75	Negative	27.5	6.50	1.7	3.0	Decreased
9	6.1	149	ND	13.7	3.72	1.3	Rare	Decreased
10	10.7	29	ND	15.6	2.93	1.9	0	Decreased
11	6.7	140	Trace	36.1	10.60	9.9	0	209
12	7.5	125	3+	10.1	10.60	8.8	Rare	28
13	13.5	66	3+	17.5	1.74	1.2	0	Decreased
14	4.7	85	ND	38.5	16.32	14.5	0	Adequate
15	12.2	56	3+	19.2	7.90	3.8	0	122
16	9.6	119	Trace	15.6	7.66	6.7	Rare	Adequate
Mean	9.0	85	ND	22.0	8.20	6.1	—	—
Reference Interval	2.2–6.2	96–248	Negative	31.7–48.0	4.00–18.70	2.3–14.0	0	175–600

*ND indicates not done.

(nos. 3 and 6). A monoclonal spike was observed in the beta region in cat 3 and in the gamma region in cat 6.

Four cats (nos. 1, 3, 11, and 16) were diagnosed with renal failure based on increased urea (32–56 mg/dL, reference interval 15–29 mg/dL) and creatinine (2.1–3.4 mg/dL, reference interval 0.5–2.0 mg/dL) concentrations, accompanied by inadequately concentrated urine in the presence of dehydration. One cat (no. 2) had increased creatinine concentration (2.9 mg/dL), a urea concentration within the reference interval (29 mg/dL), and a urine specific gravity of 1.024, despite clinical dehydration.

Seven of 14 cats had aspartate aminotransferase activities >2 times the upper limit of the reference interval, with results ranging from 82 to 420 U/L (reference interval 1–37 U/L). Cat 6 had concurrent increases in alanine aminotransferase (222 U/L, reference interval 33–152 U/L) and alkaline phosphatase (244 U/L, reference interval 22–87 U/L) activities, and hyperbilirubinemia (2.2 mg/dL, reference interval 0.1–0.8 mg/dL).

Three of 15 cats tested had hypercalcemia at initial presentation. Cats 1 and 16 had total calcium concentrations of 14.6 and 13.5 mg/dL (reference interval 9.1–11.2 mg/dL) and ionized calcium concentrations of 1.61 and 1.68 mmol/L (reference interval 1.12–1.40 mmol/L), respectively. Cat 9 had a total calcium concentration of 12.9 mg/dL; ionized calcium was not determined. Hyperphosphatemia was found in 3 cats (nos. 7, 8, and 11), with phosphorus values ranging from 6.1–8.8 mg/dL (reference interval 2.5–6.0 mg/dL).

Twelve of 16 cats had mild to severe anemia (Table 2), all but one of which were nonregenerative, normocytic, and normochromic. Cat 7 had severe regenerative, macrocytic hypochromic anemia, with 2+ polychromasia; however, the cause of the anemia was not determined. Intratubular pigment casts, interpreted as presumptive evidence of hemoglobinuria, were seen in tissue sections taken at necropsy, so intravascular hemolysis was suspected.

Five cats were neutropenic (Table 2). One cat (no. 5) had mild leukocytosis due to mild neutrophilia, concurrent with myeloid hyperplasia in the marrow aspirate. Cat 4, with a neutrophil count within the reference interval, had mild toxic change in its neutrophils. Neutrophil morphology was unremarkable in all remaining cats and there was no antemortem evidence of infection, other than periodontal disease, which was clinically assessed as incidental.

Plasma cells were detected in peripheral blood from 4 cats. Cat 8 had a leukocyte count within the reference interval but had 53% (3,000 cells/μL) plasmablasts and plasma cells (Figure 1). Cat 9 was both leukopenic and neutropenic, and had occasional moderately immature lymphocytes and well-differentiated plasma cells (<1% of total leukocytes) in peripheral blood. Cats 12 and 16 had total leukocyte and neutrophil counts within reference intervals and rare mature plasma cells.

Cat 4 was presented for intermittent epistaxis, but platelets were judged to be adequate on smear evaluation. In 2 cats in which prothrombin time and partial thromboplastin

Table 3. Paraproteins and neoplastic involvement of bone marrow and extramedullary tissues in 16 cats with multiple myeloma.

Cat No.	Bence-Jones Proteinuria	M-protein	Bone Lesion	Spleen	Liver	Lymph Node	Cutaneous Plasma Cell Tumor	Bone Marrow Plasma Cells, %	Plasma Cells with Atypia, %	Flame Cells
1	−	Biclonal	+	ND*	ND	ND	−	37	4	Few
2	ND	Monoclonal	−	+	ND	ND	−	17	48	Many
3	+	ND	+	ND	ND	ND	−	13	83	−
4	−	Monoclonal	−	+	ND	ND	−	14	79	−
5	+	Monoclonal	+	ND	ND	ND	Multiple	>80	49	Many
6	+	Biclonal	−	+	+	ND	−	ND	89	−
7†	ND	Monoclonal	+	+‡	+‡	+‡	−	>75‡	ND‡	−
8	+	Monoclonal	−	ND	ND	+	Single‡	73	34	−
9†	ND	ND	ND	+‡	+‡	+‡	−	>75‡	ND‡	−
10	ND	Monoclonal	−	ND	ND	ND	−	>80	18	−
11	−	Monoclonal	+	ND	ND	ND	−	0	−	−
12	ND	Monoclonal	−	ND	ND	ND	−	36	0	Few
13	−	Monoclonal	−	ND	ND	ND	−	21	45	−
14	−	Monoclonal	+	ND	ND	ND	−	>99‡	ND‡	−
15	ND	Monoclonal	NA	+	ND	+	−	35	11	−
16	ND	Biclonal	+	ND	ND	ND	−	78	68	−

*ND indicates not determined.

†Diagnosis of multiple myeloma made at necropsy.

‡Organ/site involvement determined histologically; all other sites determined cytologically.

time (PTT) were determined, prolongations in PTT >25% more than the control were noted.

None of the 8 cats tested for antibody to feline coronavirus had positive titers and no cats were positive for FeLV or FIV infections.

Diagnostic imaging

Thoracic and abdominal radiographs were available for review by one of the authors (AC) for 12 of the 14 cats on which radiography was performed. Eight cats (67%) had cardiomegaly; of these, 2 had pulmonary vascular enlargement and cardiogenic pulmonary edema. Hepatomegaly was seen in 7 (58%) cats and splenomegaly was seen in 4 (33%). In cat 2, renomegaly was seen in addition to hepatosplenomegaly and cardiomegaly. Cat 9 had poor peritoneal detail secondary to peritoneal effusion, which impaired evaluation of abdominal organs.

Radiographically, skeletal abnormalities were observed in 7 of the 12 cats evaluated. Cat 1 had multiple punctate lytic lesions in the femur, tibia, pelvis, and lumbar vertebrae. Cat 3 had diffuse osteopenia, based on the sclerotic appearance of the lumbar vertebral endplates and a thin double cortical line of the scapular spine. A single punctate lytic lesion was observed in the distal tibia in cat 5, in the proximal humerus in cat 7, and in the femur in cat 11. Cat 14 had a locally invasive aggressive lytic lesion in the left olecranon extending into the proximal ulnar metaphysis (Figure 2). Cat 16 had multiple small lytic lesions in the proximal humerus and cranial lum-

bar vertebrae and an expansile lesion in a rib resembling an active callus.

Ultrasound was performed in 7 cats (nos 2–7 and 9), all of which had abnormalities in the spleen. These included splenomegaly and mottled spleen (5/7), multiple hypoechoic nodules (3/7), multiple hyperechoic nodules (1/7), and diffusely hypoechoic spleen (2/7). Five of the 7 cats (71%) examined by ultrasound had 1 or more hepatic abnormalities, including hepatomegaly (3/7), diffusely hyperechoic livers (4/7); and a 7-mm in diameter hyperechoic nodule on the right lateral liver lobe and distended hepatic veins (1/7). The latter cat also had cardiomegaly and enlarged pulmonary vessels. Diffusely hyperechoic, enlarged kidneys were seen in 1 cat and enlarged hypoechoic medial iliac lymph nodes were seen in another cat.

Cytopathology and histopathology

Marrow plasmacytosis (13 to >99% plasma cells) was detected in bone marrow aspirates (11/15) or core biopsies (3/15) in 14 of the 15 cats from which diagnostic samples were obtained (Table 3). Plasma cell morphology in aspirate preparations ranged from well differentiated (2/12, 16.7%) (Figure 3) to atypical (10/12, 83.3%) (Figure 4). Atypical features included increased cell size, multiple nuclei, clefted nuclei, moderate to marked anisocytosis and anisokaryosis, variable N:C ratios, decreased chromatin density, and variably distinct, variably sized nucleoli. Plasma cells in several cats had "flame cell" morphology (Table 3), characterized by peripheral

Table 4. Summary of clinicopathologic abnormalities and diagnostic criteria in 16 cats with multiple myeloma.

Abnormality	No. Cats Affected/ No. Tested	Percentage of Cats Affected	Diagnostic Criterion
M-protein	14/14	100	Current
Splenic plasmacytosis	6/6	100	Proposed
Liver plasmacytosis	3/3	100	Proposed
Lymph node plasmacytosis	4/4	100	Proposed
Bone marrow plasmacytosis ≥10%	14/15	93.3	Current
Hyperglobulinemia	14/16	87.5	—
Atypical plasma cells	10/12	83.3	Proposed
Proteinuria	10/13	76.9	—
Anemia	12/16	75.0	—
Hypocholesterolemia	11/16	68.8	—
Bone lesion(s)	7/14	50.0	Current
Thrombocytopenia	8/16	50.0	—
Bence-Jones proteinuria	4/9	44.4	Current
Leukopenia	5/16	31.3	—
Neutropenia	5/16	31.3	—
Circulating plasma cells	4/15	26.7	—
Cutaneous plasma cell tumors	2/16	12.5	—

pink-stained cytoplasmic processes (Figure 5). In 1 cat in which multiple myeloma was diagnosed by biopsy of a lytic lesion in the left olecranon (no. 14), relatively well-differentiated plasma cells comprised almost 100% of bone marrow mass (Figure 6). Cat 11 lacked demonstrable marrow plasmacytosis, but the aspirate was taken from the radiographically unremarkable humerus, whereas the lytic lesions were detected in the pelvis and femur. Aspiration of the lytic lesions was not attempted.

Bone marrow M:E ratios were decreased in 3/11 cats and increased in 4/11. In addition to plasmacytosis, marrow changes included hemosiderosis (cats 3, 5, 9, and 10), myeloid hypoplasia (cats 1 and 10), erythroid hypoplasia (cats 5, 10, and 15), ineffective erythropoiesis (cats 2, 4, 12, and 16), ineffective erythroid hyperplasia (cat 3), myeloid hyperplasia (cat 5), and ineffective hematopoiesis (cat 13).

Noncutaneous, extramedullary tumors were detected in all 7 cats where this was assessed. Sites included spleen, liver, and lymph nodes (Table 3). The lymph nodes were mesenteric in 3 cats and both mesenteric and iliac in the cat with the single, tarsal cutaneous plasma cell tumor. Plasma cell infiltrates did not always correlate with splenomegaly, hepatomegaly, or lymphadenopathy. If enlarged organs were aspirated, they were invariably infiltrated, but myeloma cell infiltrates were also detected in organs of normal size. Five cats with ultrasonographic changes in the spleen had either histologic (1 cat at necropsy) or cytologic (4 cats) evidence of tumor involvement.

The cutaneous masses noted in cat 5 were diagnosed as plasma cell tumors by cytology. One cat (no. 9) presented with
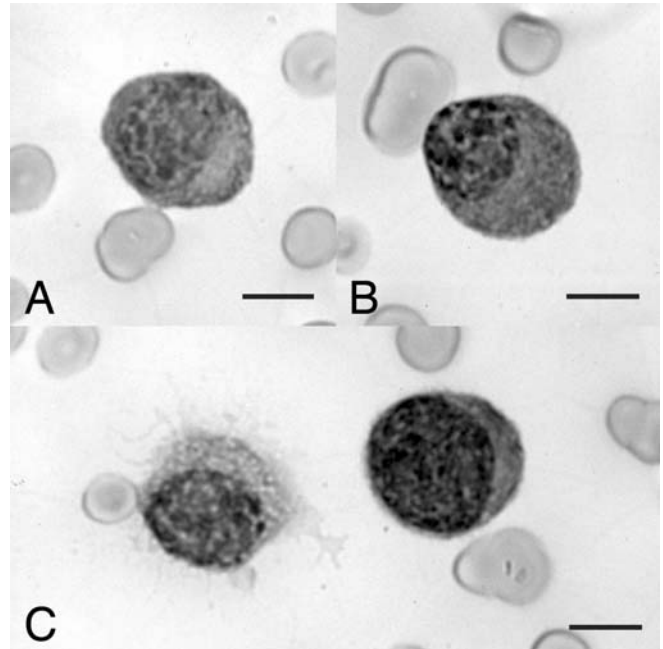

Figure 1. Peripheral blood (cat 8). (**A**) Slightly immature plasma cell with eccentric oval nucleus, moderately dense chromatin, and pronounced paranuclear clearing. (**B**) Well-differentiated plasma cell with an eccentric slightly oval nucleus, dense chromatin, and slight paranuclear clearing. (**C**) The plasma cell on the left has a small, slightly oval, eccentric nucleus, moderately dense chromatin, and scant cytoplasm with fine, wispy cytoplasmic processes. The cell on the right is larger and has a higher N:C ratio, consistent with a plasmacytoid lymphoblast or plasmablast, but chromatin is atypically dense and granular (maturation asynchrony). Wright's-Giemsa, bar=7.5 μm.

pleural and peritoneal effusions, all of which were characterized as modified transudates, with no neoplastic cells or infectious agents noted on cytologic examination.

Necropsy findings confirmed the diagnosis of multiple myeloma in cats 7 and 9. Gross lesions in cat 7 included moderate icterus, hepatosplenomegaly, cardiomegaly, and generalized lymphadenopathy. On histopathology, marked plasmacytosis was noted in bone marrow, spleen, liver, and mandibular, retropharyngeal, prescapular, and axillary lymph nodes. Plasma cells were typical to atypical with anisocytosis, anisokaryosis, decreased N:C ratios, and occasionally, binucleation. Moderate plasmacytosis also was noted in periportal areas and sinusoids within the liver. The bone marrow was hypercellular (90–95% cellularity) with typical and atypical plasma cells distributed unevenly among normal marrow elements; plasma cell mass comprised approximately 50% of bone marrow mass. Cat 9 was emaciated, with moderate fibrinous peritoneal effusion and severe serosanguinous pleural effusion. Superficial, mesenteric, bilateral iliac, and cranial mediastinal lymph nodes were moderately to severely enlarged, and hepatosplenomegaly and cardiomegaly were noted. Marked infiltration of typical and atypical plasma cells was detected on histopathologic sections of bone marrow, spleen, and lymph nodes. Atypical cells were similar to those described in case 7. In the bone marrow, plasma cells were

Figure 2. Lateral radiograph of the left elbow (cat 14). A locally invasive aggressive lytic lesion affects the olecranon and proximal ulna. Notice the multiple round to oval lytic areas and the pathologic fracture of the olecranon. Biopsy of this lesion (see Figure 6) revealed numerous plasma cells.

unevenly distributed among normal marrow elements, comprising 15–60% of bone marrow mass. In addition, chronic diffuse epicardial fibrosis was observed, most likely unrelated to the multiple myeloma, as was possible terminal bacteremia, possibly associated with the neutropenia present at the time of death.

Diagnostic summary and outcome

Eight of the 16 cats fulfilled 2 of the 4 criteria required for antemortem diagnosis of multiple myeloma (Tables 3, 4). Six cats met 3 of the criteria and 1 cat met all 4 criteria. Multiple
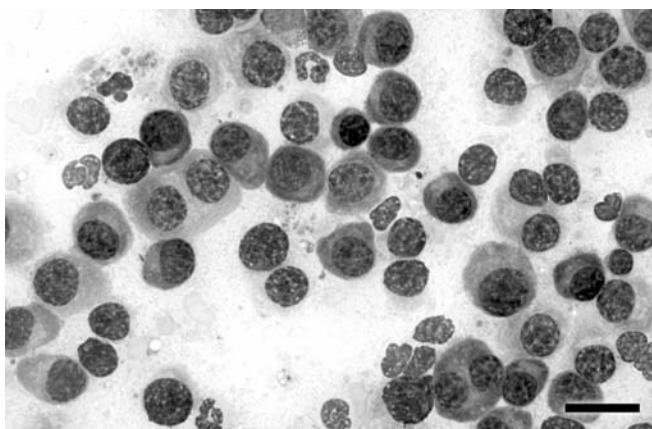

Figure 3. Fine needle aspirate of spleen (cat 2). Well-differentiated plasma cells, bare nuclei, and a few neutrophils are seen. Two of the plasma cells are binucleated. Wright's-Giemsa, bar=15 µm.
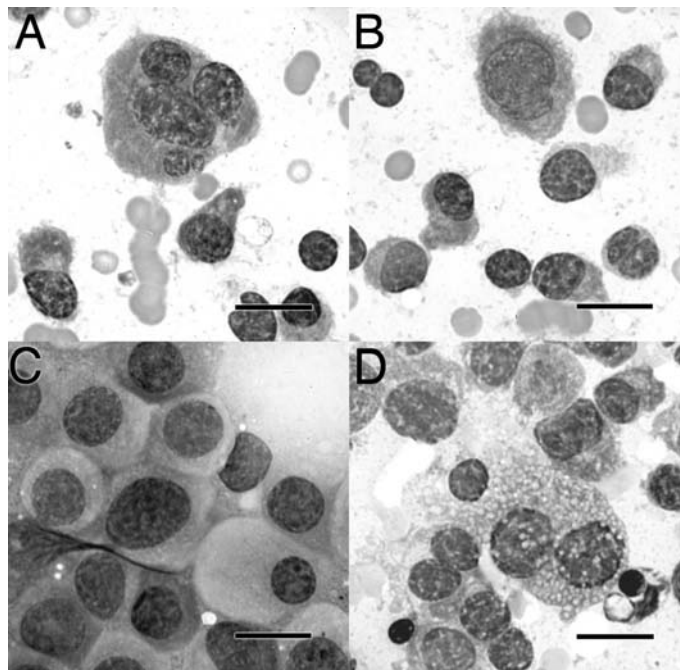

Figure 4. Multiple myeloma characterized by plasma cells with atypical morphology. (**A**) Fine needle aspirate of the spleen (cat 4). A very large multinucleated plasma cell with marked anisokaryosis and 2 micronuclei. Three small plasma cells and 2 bare nuclei also are seen. (**B**) Fine needle aspirate of the spleen (cat 4). Atypical plasma cells characterized by binucleation, atypical nuclear and cytoplasmic contours, variable N:C ratios, marked anisokaryosis, and marked anisocytosis. (**C**) Cranial thoracic mass aspirate (cat 5). Several plasma cells have variable N:C ratios, marked anisokaryosis, and moderate anisocytosis. (**D**). Bone marrow aspirate (cat 8). Plasma cells have cytoplasmic vacuolization, binucleation, and marked anisocytosis and anisokaryosis. Wright's-Giemsa, bars=7.5 µm.

myeloma in 1 cat was diagnosed by necropsy; plasma cell tumors were found in bone, spleen, liver, and lymph nodes. Four cats (nos. 3, 4, 7, and 9) were euthanized with no treatment because of their deteriorating condition either at the time of diagnosis or several days later. Four cats (nos. 1, 2, 6, and 16) were lost to follow-up. Cat 14 underwent removal of the lytic olecranon with no additional treatment and was still alive at the time of writing. Seven cats were treated with prednisone and melphalan. Of these, 5 cats (nos. 10–13 and 15) survived 4 to 8 weeks, 1 cat (no. 8) survived 4 months, and 1 cat (no. 5) survived 6 months from the time of diagnosis. Deaths in all 7 treated cats were by euthanasia.

Discussion

Multiple myeloma is an uncommonly diagnosed disease in cats and has been reported infrequently in the literature. The cats in this report bring the total number of reported feline multiple myeloma cases to 47.[1,3–15] We determined the frequency of multiple myeloma in cats at MJR-VHUP to be slightly <1% of all malignant neoplasms in cats during the
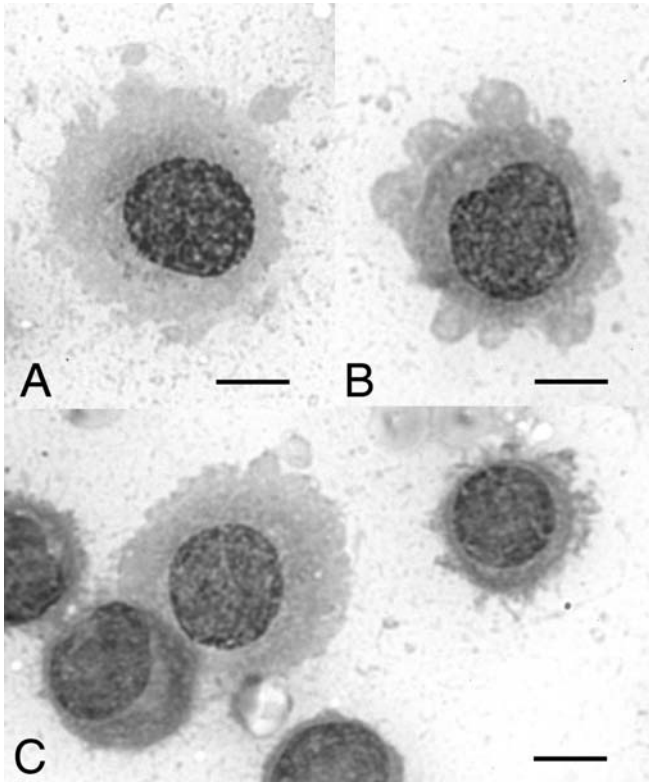
Figure 5. Xiphoid mass aspirate (cat 5). (**A, B, C**) Plasma cells with flame cell morphology, characterized by irregular and fragmented or blunt and rounded pink-stained cytoplasmic projections. Wright's-Giemsa, bar=7.5 μm.

same time period. Canine multiple myeloma during the same time period at MJR-VHUP was diagnosed at a much lower frequency, accounting for only 0.3% of all malignancies in dogs (McManus P, unpublished data). Absolute numbers of canine cases outnumbered feline cases during these 8 years, but only because our hospital sees a substantially higher number of canine patients. Multiple myeloma accounted for approximately 2% of all hematopoietic neoplasms in both dogs (McManus P, unpublished data) and cats at our hospital. This incidence was higher than that previously reported, but still is much less than the rate in humans, where multiple myeloma is the second most common hematopoietic neoplasm, accounting for 13% (Caucasians) to 33% (African Americans) of all hematopoietic tumors.[20] Multiple myeloma is extremely rare in other domestic species with only a few reported cases in horses.[21–29]

Multiple myeloma is generally a disease of older animals. Only 4 cats in our study were <10 years old, and the average age was 12.5 years. In people, the average age at diagnosis is 66 years.[30] In our study of 16 cats, males accounted for 56% of cases. Pooling information from previous reports, males account for 63.8% (30/47) of all feline multiple myeloma cases. This sex predisposition is similar to what occurs in people, where the largest retrospective study, of 1027 patients, included 59% men.[30] There is no apparent gender predilection in dogs; the largest retrospective study to date (60 dogs)
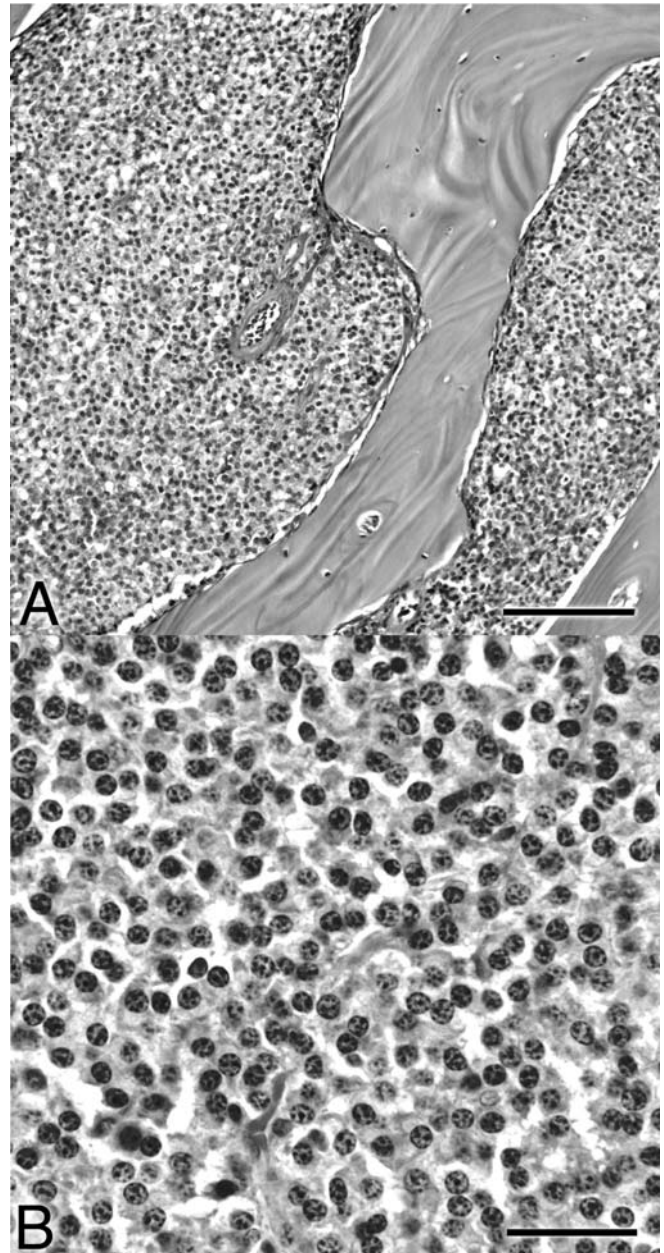

Figure 6. Biopsy of a lytic lesion in the left olecranon (cat 14). Sheets of well-differentiated plasma cells fill the bone marrow spaces. H&E, (**A**) bar=50 μm; (**B**) bar=20 μm.

included 30 males and 30 females.[31] As in other species, multiple myeloma is not likely to be directly caused by a specific viral infection. A link between human immunodeficiency virus and progression to multiple myeloma has not been established,[32,33] and cats in this study were negative for FIV and FeLV infection.

The results of this study reinforced the impression that clinical signs of feline multiple myeloma, as in other species, are usually nonspecific, eg, lethargy, vomiting, renal failure, hemostatic abnormalities, anorexia, and diarrhea. The first

clue to a diagnosis is usually hyperglobulinemia, which was found in 87.7% of animals in this study.

Current published recommendations for determining a diagnosis in animals initially appear straightforward, in that 2 of the following 4 criteria are required: 1) bone marrow plasmacytosis with >20% plasma cells, 2) monoclonal gammopathy based on SPE, 3) osteolysis, and 4) light chain (Bence-Jones) proteinuria.[2] These criteria are unweighted for animal patients; in people, criteria are weighted as "major" and "minor" and accommodate lower plasma cell percentages.[17] In people, confirmation of myeloma requires first that the patient be symptomatic (ie, have bone pain) or have anemia, hypercalcemia, azotemia, hypoalbuminemia, or bone demineralization. The diagnostic criteria of multiple myeloma are then applied. Major criteria include 1) plasmacytoma(s) with biopsy, 2) marrow plasmacytosis >30%, 3) M-protein with >3.5 g/dL IgG or >2.0 g/dL IgA, and 4) kappa or lambda light chain excretion >1.0 g/dL on 24-hour urine protein electrophoresis. The 4 minor criteria include a) marrow plasmacytosis with 10–30% plasma cells, b) M-protein at values less than indicated above, c) lytic bone lesions, and d) <50% normal serum Ig concentration. If the diagnosis includes major criteria, then any 2 of the 4 will suffice, or major criterion 1 plus minor criterion b, c, or d; or major criterion 3 plus minor criterion a or c. If the diagnosis is based on only minor criteria, then it must include the first and second criteria (a and b), plus 1 of the remaining 2 criteria (c or d). In our study we didn't imitate this system, but we did modify the requirements for animals by including plasma cell atypia as a criterion when marrow plasmacytosis was between 10 and 20%, which occurred in 3 cases. In humans, nuclear-cytoplasmic maturation asynchrony, nuclear immaturity, and pleomorphism are considered reliable markers for distinguishing neoplastic cells from reactive plasma cells.[16,17] In addition, reactive plasma cells usually do not exceed 5% of all nucleated cells in marrow and are well differentiated.[16–18]

Although we required a minimum of 10% marrow plasmacytosis for diagnosis, it should be noted that even the 10% threshold can be problematic because enumeration of plasma cells in routinely stained bone marrow aspirate smears may significantly underestimate plasmacytosis when compared to immunohistologic examination.[34] In a study of 176 human patients with multiple myeloma, where diagnosis was based on immunohistologic techniques, 40% of patients had <10% plasma cells in bone marrow aspirates.[34]

Using the modified guidelines described here, the most commonly paired criteria in cats were marrow plasmacytosis and paraproteinemia, which were found in 12 of 16 cats. Of the remaining 4 cats, 1 lacked a marrow aspirate and 2 lacked SPE. Only 1 cat lacked demonstrable marrow involvement, and the diagnosis was based on lytic lesions and a monoclonal spike. Results of bone marrow evaluation were normal, but the aspirate had been taken some distance away from the lytic lesions. This negative marrow result likely reflected the focal nature of multiple myeloma and served to emphasize the importance of a core biopsy or multiple marrow aspirates from different sites, particularly affected bone sites. Although we did not use extramedullary involvement as a diagnostic criterion, it was a common finding in the cats in this study,

suggesting that assessment of extramedullary sites could assist in the diagnostic evaluation of hyperglobulinemic cats, especially when marrow aspirates cannot be obtained. This is in contrast to dogs, where extramedullary involvement is a less consistent finding (Van Winkle T, unpublished observations based on MJR-VHUP necropsy reports for canine multiple myeloma).

Using the 4 criteria as currently defined in veterinary medicine could potentially result in a diagnosis of multiple myeloma based only on the presence of an M-protein and light chain proteinuria, raising the question as to whether these criteria are sufficient. In this study, 1 cat met only these 2 criteria; however, bone marrow aspirates were not done because both liver and spleen were infiltrated with plasma cells. In such cases, perhaps an M-protein and light chain proteinuria should be considered together as constituting 1 criterion rather than separate entities, and, as discussed previously, plasma cell atypia and extramedullary involvement should be included to assist in diagnosis.

The presence of a monoclonal protein (M-protein or M-spike) reflecting production of a single Ig is one of the most discriminating clues that a plasmacytosis is neoplastic, ie, clonal, as opposed to reactive. In people, an M-protein is found in the serum or urine of >97% of myeloma patients,[30] with remaining cases classed as nonsecretory. In the 14 cases in which SPE was performed in our study, 11 (78.5%) had monoclonal proteins, and 3 had biclonal spikes (21.4%), all migrating in the gamma region. Possible causes for paired spikes include 2 independent secretory tumor cell lines,[35] the divergence of the primary tumor into 2 separate plasma cell populations producing distinct M-proteins, 1 clone of myeloma cells producing 2 distinct paraproteins, or spurious biclonal peaks due to split dimeric or multimeric paraproteins, eg, IgA.[4]

Multiple myeloma is the most common cause of M-proteins; however, other conditions occasionally can induce a monoclonal gammopathy in small animals, such as chronic infection (leishmaniasis,[36,37] ehrlichiosis,[37–40] chronic pyoderma,[41] feline infectious peritonitis), amyloidosis, B-cell lymphoma,[37] Waldenströms macroglobulinemia,[37,42] and MGUS.[43] Our study included a cat with a history of monoclonal gammopathy but no abnormal physical, hematologic, chemical, or radiographic findings at the time of first detection. This cat met all criteria for a diagnosis of MGUS, which includes M-protein and <10% bone marrow plasmacytosis, with no evidence of lytic lesions, light chain proteinuria, or other clinical, hematologic, and biochemical abnormalities.[44,45] MGUS occurs in 1–2% of people over the age of 50 and in 3% of people over the age of 70.[44,45] A significant proportion (25%) of these will evolve within 20 years into multiple myeloma, primary amyloidosis, macroglobulinemia, or another lymphoproliferative disease.[45] To the authors' knowledge, this is the first reported case of MGUS in a cat. This cat first developed MGUS as a young adult of 4 years old, and it took almost half of the cat's lifetime (9 years) to progress to multiple myeloma.

Diagnostic criteria in veterinary medicine do not currently hinge on determination of the type of Ig; therefore, clinicians in our hospital rarely request this test. Only 2 of the

cats in this study (1 with IgA and 1 with IgG) had Ig type determined. Of the 25 published feline myeloma cases with immunoelectrophoresis results, including the 2 cases above, 20 had IgG gammopathies, and 5 had IgA gammopathies.[1,3,4,6]

Common manifestations of bone lesions in multiple myeloma in both people and animals include classic punched-out lytic areas, generalized osteopenia, and pathologic fractures.[30] In this study, the percentage of cats with radiographically-evident skeletal lesions was 58.3%, which was higher than the 20% previously described for cats,[3,4,13,15,46] but similar to the 50–56% occurrence reported for dogs.[15,31] The reason for the difference in our study compared to previous studies in cats may be increased clinician awareness of the lesion, better quality radiographs, and increased knowledge about the disease. The focal lytic lesions reported in cats affect pelvis, ribs, vertebral columns, and long bones, whereas humans also have skull lesions.[17] Skull films were not done for any of the 16 cats. Other causes of focal osteolysis are rare, and include carcinomas,[47] giant cell tumors of bone,[48] benign aneurysmal bone cysts,[49–51] and bone lesions secondary to tumor invasion.[51–53] One cat had generalized osteopenia, which was diagnosed radiographically. Demineralization of bone in humans is detected through measurement of bone mineral density, a technique not used routinely in the assessment of animals. Generalized osteopenia is not specific for multiple myeloma and may be seen with nutritional, renal, and metabolic disorders.[54–57]

Multiple myeloma–associated hypercalcemia is not reported as frequently as bone lysis,[15,30,31] perhaps because disease progression is usually slow, allowing for appropriate metabolic controls. In our study, 20% of cats were hypercalcemic based on total calcium concentration. An ionized calcium test is needed to confirm hypercalcemia, because binding of calcium by the M-protein will increase total calcium concentration while ionized calcium remains within normal limits.[13] Increased ionized calcium concentration, as seen in 2 of the cats in this study, supports true hypercalcemia. Paraneoplastic hypercalcemia can result from lysis of bone either by tumor expansion or by osteoclast activation.[13] A recent retrospective study of 71 cases of hypercalcemia in cats over a 6-year period found that neoplasia (primarily lymphoma and squamous cell carcinoma), renal failure, and urolithiasis were the most commonly seen causes of increased total calcium concentration. None of the cats with neoplasia was diagnosed with multiple myeloma.[58] This likely reflects the low prevalence of this disease, rather than the frequency of hypercalcemia in myeloma patients, which, given the results of our study, is probably higher for myeloma than for any other feline neoplasm.

Light chain proteinuria was noted in 44.4% of cats in our study. Taking into account these 9 cases plus previously reported cases, light chain proteinuria is found in 64.7% of feline multiple myeloma patients.[1,3,4,59] Screening for light chain proteinuria should not be limited to the urine dipstick method for proteinuria, because dipsticks primarily detect albuminuria. The SSA test is more sensitive to globulins and thus can be positive when the dipstick is negative, but it is nonspecific in that it detects albumin, globulins, Bence-Jones protein, polypeptides, and proteases.[60] False-positive SSA results may occur with penicillin and its derivatives, tolbutamide or sulfisoxazole metabolites, or certain roentgenographic contrast media in the urine.[60] In people, it has been reported that false-positive results for Bence-Jones proteins, assayed by heat precipitation, may be due to an excess of polyclonal light chains in patients with connective tissue diseases, chronic renal failure, or nonplasmacytic malignancies.[61] For these reasons, protein electrophoresis of concentrated urine is the preferred technique for detection of monoclonal light chains in urine.[2,61]

There are limited reports on the radiographic and ultrasonographic findings of internal organs in feline multiple myeloma. Radiographic abnormalities in this study included hepatomegaly (58.3%), splenomegaly (25.0%), cardiomegaly (66.6%), and renomegaly (9.0%). The differential diagnoses for each individual finding is extensive and rarely includes multiple myeloma, but for hepatomegaly, splenomegaly, and cardiomegaly in combination with history and blood test results, the list is shorter. Common neoplastic conditions that can produce this triad of organomegaly in cats include lymphoma and mast cell tumors. In this study we demonstrated that feline multiple myeloma, although not common, also induces these radiographic changes. Cardiomegaly and cardiac disease, if present, may be explained by excessive cardiac workload and myocardial hypoxia secondary to hyperviscosity, as previously described in people.[62]

The most common ultrasonographic abnormalities involved the spleen and liver and to a lesser extent the kidneys. The most consistent finding was splenic enlargement and diffuse or nodular hypoechogenicity. Aspiration cytology or biopsy of ultrasound-detected splenic lesions was always diagnostic for plasma cell infiltration. Even though a small number of cats was evaluated in this study, these ultrasonographic changes may be an important new finding that contributes to fast and accurate diagnoses of plasma cell neoplasms because of the ease and low morbidity and mortality from fine needle aspiration of spleen. Although not a common disease in cats, plasma cell myeloma should be added to the list of differential diagnoses for an enlarged, mottled, hypoechoic spleen. The most consistent hepatic abnormality was diffuse hyperechogenicity and enlargement. The most common causes for a diffusely hyperechoic liver in cats are lipidosis and lymphoproliferative disease. Hepatic lipidosis could not be ruled out as a contributing factor in most of the cats in this study, especially with the history of anorexia and lethargy; however, 1 cat with hyperechoic liver had diffuse infiltration of malignant plasma cells on necropsy and no evidence of hepatic lipidosis.

Hypocholesterolemia affected 68.7% of cats in this study, far more than the 26% reported for human patients.[30] Serum cholesterol concentration is thought to correlate inversely with globulins concentration.[30] Cat 4, for example, had one of the highest globulin concentrations (12.5 g/dL) and one of the lowest cholesterol concentrations (45 mg/dL). One postulated explanation is down-regulation of cholesterol production by the liver to maintain oncotic pressure in the face of hyperglobulinemia.[63] No cats had evidence of protein–losing enteropathy or severe malnutrition as a cause for decreased cholesterol, and only cat 6 had evidence of hepatic functional

insufficiency. Hypocholesterolemia can be seen with hyperthyroidism; however, none of the cats in this study were tested for total or free T4 concentration.

Complications secondary to hyperglobulinemia include hyperviscosity syndrome (HVS) and coagulation defects. Typical signs of hyperviscosity include seizures, congestive heart failure, and retinal hemorrhages.[6] IgA and IgM are more often associated with HVS, because IgA can dimerize or polymerize and IgM is a pentamer. HVS has been reported previously in 4 of 11 cats in which retinal hemorrhages, neurologic signs, or both were noted.[6,8] Three had IgG gammopathies, and 1 had IgA gammopathy. One cat in this study had hyperviscous serum; however, immunoelectrophoresis was not done to determine the type of Ig. Cat 7 had bilateral retinal hemorrhages and a prolonged PTT, signs consistent with hyperviscous serum; however, serum viscosity was not measured. Coagulation defects can result from paraprotein interference with clotting factors, protein coating of platelets leading to thrombocytopathy, and binding of the Fab fragment of the M-protein to fibrin, preventing aggregation.[64,65] Only 1 cat in this study was suspected clinically of having coagulopathy (epistaxis), but the results of a coagulation profile and platelet count were unremarkable. Unfortunately, platelet aggregation studies were not done. Other causes for coagulation defects include decreased platelet production by infiltrated marrow, increased platelet consumption, or increased platelet destruction. Just over half of the cats in this study had thrombocytopenia, 1 of which also had prolonged PTT.

Increased susceptibility to infection is common in human patients with multiple myeloma, and is potentially life-threatening.[66] Infectious processes in this study included 1 cat each with severe periodontitis, chronic recurrent upper respiratory infections, and terminal bacteremia. Multiple myeloma–associated immunodeficiency is likely a multifaceted phenomenon secondary to decreased production of functional Ig,[67] suppression of normal B-cell differentiation and function[68] in response to antigenic stimulation,[69] increased rate of gamma globulin catabolism, or neoplastic infiltration of bone marrow resulting in leukopenia.[70]

Unusual cases in our study included 2 cats with cutaneous plasma cell tumors. Solitary cutaneous plasma cell tumors usually are not aggressive, and reports of metastasis are rare.[46,71,72] One cat not only had metastasis but met the criteria for both multiple myeloma and plasma cell leukemia (PCL). PCL is an extremely rare disease in any species, and there have been no reports to date in cats, other than this case, published previously as a single case report.[73] Two forms of PCL are defined in people: primary, in which there is no previous diagnosis of myeloma, and secondary, in which PCL is a late manifestation of previously diagnosed multiple myeloma or plasmacytoma (as seen in cat 8). Regardless of whether primary or secondary, diagnosis of PCL requires ≥20% marrow plasmacytosis and >2000 plasma cells/µL in peripheral blood. Cat 8 met these criteria. In a study of 826 human myeloma patients, plasma cells were observed in peripheral blood smears of 16%, but most of these failed to meet the criteria for PCL.[63] Similarly, we had 2 cases with circulating plasma cells, but in insufficient numbers to warrant

a diagnosis of PCL. Plasma cell leukemia in human patients is associated with a very poor prognosis because it follows a course similar to other acute leukemias[74] and is poorly responsive to chemotherapy.[75]

In summary, the most common abnormalities seen in this retrospective study of cats with multiple myeloma included paraproteinemia, bone marrow plasmacytosis, atypical plasma cell morphology, hypocholesterolemia, bone lysis, anemia, and multi-organ involvement. A moderate number of cats had light chain proteinuria, thrombocytopenia, and neutropenia. Rare abnormalities include HVS, hypercalcemia, hypoalbuminemia, cutaneous tumors, and PCL. Our findings suggest that successful analysis of bone marrow aspirates and serum protein concentrations should be sufficient to establish a diagnosis of multiple myeloma in cats; however, we advocate modifying the diagnostic criteria to include visceral organ infiltration and atypical plasma cell morphology, especially when the percentage of plasma cells in the marrow is <20%. Allowance for atypical morphology or detection of plasmacytosis at additional sites may assist in the diagnosis of otherwise difficult cases.

Authors' Note in Addendum

Since acceptance of this article, 4 additional cases of feline multiple myeloma were diagnosed at MJR-VHUP. All 4 had hepatic involvement, and 3 had splenic involvement (the spleen of 1 cat was not evaluated). These observations emphasize the advantage of assessing extramedullary sites in cats suspected of having multiple myeloma. Furthermore, all 4 cats were hypocholesterolemic, 2 were hypercalcemic, and 1 had multiple lytic lesions, similar to the cats in this study.

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