Case Report

Progression of a solitary, malignant cutaneous plasma-cell tumour to multiple myeloma in a cat

A. Radhakrishnan¹, R. E. Risbon¹, R. T. Patel¹, B. Ruiz² and C. A. Clifford³

¹ Mathew J. Ryan Veterinary Hospital of the University of Pennsylvania, Philadelphia, PA, USA
² Antech Diagnostics, Farmingdale, NY, USA
³ Red Bank Veterinary Hospital, Red Bank, NJ, USA

Abstract
An 11-year-old male domestic shorthair cat was examined because of a soft-tissue mass on the left tarsus previously diagnosed as a malignant extramedullary plasmacytoma. Findings of further diagnostic tests carried out to evaluate the patient for multiple myeloma were negative. Five months later, the cat developed clinical evidence of multiple myeloma based on positive Bence Jones proteinuria, monoclonal gammopathy and circulating atypical plasma cells. This case represents an unusual presentation for this disease and documents progression of an extramedullary plasmacytoma to multiple myeloma in the cat.

Keywords
hyperproteinaemia, monoclonal gammopathy, multiple myeloma, pancytopenia, plasmacytoma

Introduction
Plasma-cell neoplasms are rare in companion animals. They represent less than 1% of all tumours in dogs and are even less common in cats (Weber & Tebeau, 1998). Diseases represented in this category of neoplasia include multiple myeloma (MM), immunoglobulin M (IgM) macroglobulinaemia and solitary plasmacytoma (Vail, 2001). These conditions can result in an excess secretion of Igs (paraproteins or M-component) which produce a monoclonal spike via serum protein electrophoresis.

MM is a systemic proliferation of neoplastic plasma cells from the bone marrow. Consequences of the systemic disease include bone pathology (lysis), hyperviscosity syndrome, blood dyscrasias, cytopenias and organ failure (MacEwen & Hurvitz, 1977). M-component elevation may lead to hyperviscosity syndrome, characterized by increased serum viscosity, blood sludging and poor oxygen delivery to tissues. Hyperviscosity occurs more commonly with IgM macroglobulinaemia, although it also can occur with IgG or IgA hypersecretion (Matus & Leifer, 1985; Dorfman & Dimski, 1992). Clinical signs of hyperviscosity include coagulopathy, neurologic signs (dementia and ataxia), dilated retinal vessels, retinal haemorrhage or detachment, and cardiomyopathy (Dorfman & Dimski, 1992; Forrester et al., 1992). Coagulopathy can result from the M-component interfering with the normal function of platelets or clotting factors. Renal dysfunction is often associated with MM and may be the result of damage by Bence Jones proteins, tumour infiltration, hypercalcaemia, amyloidosis or decreased perfusion (MacEwen & Hurvitz, 1977). Other clinical manifestations of MM include polyuria or polydipsia secondary to hypercalcaemia or renal failure, spinal pain and pathologic fractures. A diagnosis of MM requires at least two of four criteria: (1) greater than 20% plasma cells in the bone marrow, (2) monoclonal gammopathy, (3) osteolytic lesions and (4) Ig light chains (Bence
Jones protein) in the urine (Drazner, 1982; Eastman, 1996; Weber & Tebeau, 1998; Bienzle et al., 2000).

In contrast to MM, plasmacytomas are solitary tumours containing neoplastic plasma cells. In dogs, two types of plasmacytomas have been described: extramedullary and solitary osseous forms that originate from soft tissue and bone, respectively. Extramedullary plasmacytomas are commonly cutaneous and typically benign, and surgical excision is often curative (Mandel & Esplin, 1994). Non-cutaneous extramedullary plasmacytomas tend to be more aggressive and are commonly associated with gastrointestinal tract, and typically, there is metastasis to the local lymph nodes (Brunnert et al., 1992; Trevor et al., 1993; Jackson et al., 1994). Systemic progression to MM is not typical with extramedullary plasmacytomas (Vail, 2001). Osseous plasmacytomas occur in long bones, vertebral bodies, the zygomatic arch and ribs. In dogs, solitary osseous plasmacytomas can progress to MM (MacEwen et al., 1984).

There is a paucity of information in the veterinary literature regarding plasmacytoma and MM in the cat (Carothers et al., 1989; Forrester et al., 1992; Larsen & Carpenter, 1994; Mandel & Esplin, 1994; Eastman, 1996; Sheafor et al., 1996; Weber & Tebeau, 1998; Zikes et al., 1998; Bienzle et al., 2000; Hickford et al., 2000). In the cat, MM carries a poor prognosis, particularly when compared with plasmacytomas, which may respond to surgery alone (Mandel & Esplin, 1994). Cats with MM do not typically develop osseous lesions nor do they commonly develop solitary osseous plasmacytomas (Weber & Tebeau, 1998). Although case reports exist documenting plasmacytoma with a monoclonal gammopathy (Carothers et al., 1989; Larsen & Carpenter, 1994; Mandel & Esplin, 1994), to the authors’ knowledge, progression of a solitary plasmacytoma to MM has not been reported in the cat. This report describes a cat with a solitary extramedullary plasmacytoma that progressed to MM.

Clinical report

An 11-year-old intact male domestic shorthair cat was examined by the local veterinarian for a mass around the left tarsus. Physical examination revealed four lobulated, soft-tissue masses that encompassed the tarsus circumferentially. Radiographs of the affected extremity revealed no evidence of osteolysis. Complete blood count (CBC) and serum chemistry results were unremarkable. Segmental resection was carried out to remove two of the lateral masses. Histopathology revealed a poorly differentiated polymorphous blastic-type malignant plasma-cell tumour that stained positively for amyloid. Serum protein electrophoresis, whole-body radiographs (thorax and abdomen) and bone marrow aspiration were carried out to further investigate the extent of disease. Serum protein electrophoresis revealed a mild elevation of alpha-2 globulin concentration (1.65 g dL\(^{-1}\), reference interval 0.2–1.5), consistent with an inflammatory process. Radiographs revealed no evidence of osteolytic lesions. Cytologic examination of a bone marrow aspirate was interpreted as erythroid hypoplasia, with only rare macrophages and plasma cells reported.

The patient was transferred to a referral centre 4 months later for further staging to rule out abdominal organ involvement in anticipation of radiation therapy. CBC and serum chemistry results again were unremarkable. Abdominal ultrasonography revealed an enlarged medial iliac lymph node. Fine-needle aspiration of the lymph node was consistent with metastatic plasma-cell tumour (Fig. 1). Based on the diagnosis of metastasis from the original solitary plasmacytoma, the patient was referred to the oncology service of the Veterinary Hospital of the University of Pennsylvania, approximately 6 months after the initial identification of the mass and 4 months after the initial workup for MM.

At presentation, the owner reported no clinical abnormalities, with the exception of the soft-tissue mass overlying the tarsus. Physical and ophthalmoscopic examinations were otherwise unremarkable. The cat’s body weight was 8.04 kg. Measurements of the mass were slightly greater than those taken 2 months earlier. A CBC indicated a normal leucocyte count (5.65 K m\(^{-1}\), reference interval 4.0–18.7), neutropenia (0.760 K m\(^{-1}\), reference interval 2.30–14.0), normocytic, normochromic anaemia (hematocrit 27.5%, reference interval 31.7–48.0) and thrombocytopenia (platelet count 55.1 K m\(^{-1}\), 37

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Cytologic review of the blood smear revealed 53% (2.99 K\text{mL}^{-1}) of the leucocytes to be atypical plasma cells (Fig. 2). Abnormalities on serum chemistry included hyperproteinaemia (11.7 g dL\text{L}^{-1}, reference interval 6.0–8.6), hyperglobulinaemia (8.4 g dL\text{L}^{-1}, reference interval 2.2–6.2), hypernatraemia (162 mmol L\text{L}^{-1}, reference interval 146–157) and elevated aspartate aminotransferase activity (59 U L\text{L}^{-1}, reference interval 1–37). Bence Jones proteins were detected in the urine with classical heat precipitation methods. A monoclonal spike was detected within gamma globulin fraction (3.73 g dL\text{L}^{-1}, reference interval 0.5–1.90) on serum protein electrophoresis. Ig quantification by radial immunodiffusion identified an IgA gammopathy (IgA concentration >2000 mg dL\text{L}^{-1}, reference interval 102–582). Radiographs of the thorax and abdomen revealed no evidence of osteolytic lesions. The bone marrow aspirate was haemodiluted precluding definitive analysis, but 73% of the nucleated cells (500 cell differential count) were atypical plasma cells. Based upon the monoclonal gammopathy, Bence Jones proteinuria and atypical plasma cells in blood, a diagnosis of MM was made. There was no evidence of hyperviscosity syndrome, ocular disease, renal disease or bleeding diathesis at the time of diagnosis of MM.

Therapy was initiated using melphalan (Alkeran, Glaxo Smith Kline, Research Triangle Park, NC, USA) (0.25 mg kg\text{kg}^{-1} peroral every 24 h, given for 5 consecutive days every 3 weeks), prednisone (1 mg kg\text{kg}^{-1} every 24 h) and enrofloxacin (Baytril, Bayer Corporation, Shawnee Mission, KS, USA) (5 mg kg\text{kg}^{-1} every 12 h). The cat demonstrated clinical improvement for 2 months following the onset of therapy. There was a decrease in total serum protein (9.0 g dL\text{L}^{-1}, reference interval 5.2–8.8) and

**Figure 1.** (A) Cytologic smear made from an ultrasound-guided fine-needle aspirate of an iliac lymph node from a cat. There are large round-to-ovoid neoplastic cells admixed with moderate numbers of small lymphocytes and abundant blood [Wright–Giemsa stain, bar = 40 \mu m]. (B) Two neoplastic round cells with a slight paranuclear Golgi clearing. One is binucleated, whereas the second cell shows a cleaved nucleus [Wright–Giemsa stain, bar = 5 \mu m]

**Figure 2.** Peripheral blood smear: A single plasma cell is shown. These cells constituted 53% (3000 cells \text{mL}^{-1}) of the leucocyte differential [Wright–Giemsa stain, bar = 5 \mu m]

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globulin concentrations (5.3 g dL⁻¹, reference interval 2.3–5.3) and an increase in the blood neutrophil count (1600 K μL⁻¹, reference interval 2.30–14.0).

Two and a half months after the onset of chemotherapy, the cat was examined because of severe anaemia. Abnormalities in physical examination included tachycardia (heart rate 200 min⁻¹), pale mucous membranes, grade II/VI systolic heart murmur and the mass on the left tarsus. The cat’s body weight was 6.7 kg. CBC results included leukopenia (3.06 K μL⁻¹, reference interval 4.00–18.7), macrocytic, normochromic, non-regenerative anaemia (mean corpuscular volume 54.7 fl, reference interval 36.7–53.7; mean corpuscular hemoglobin concentration 32.4 g dL⁻¹, reference interval 30.1–35.6; hematocrit 13.2%, reference interval 31.7–48.0) and thrombocytopenia (42.6 K μL⁻¹, reference interval 175–500). The reticulocyte count was 4 × 10⁶ reticulocytes μL⁻¹, with an absolute erythrocyte count of 2.13 × 10⁶ cells μL⁻¹. Serum chemistry abnormalities included hypernatraemia (163 mmol L⁻¹, reference interval 146–157), hypercalcaemia (12.1 mg dL⁻¹, reference interval 9.1–11.2) with mildly elevated ionized calcium (1.35 mmol L⁻¹, reference interval 1.13–1.33), hypermagnesaemia (3.4 mg dL⁻¹, reference interval 1.9–2.6) and hyperproteinaemia (11.7 g dL⁻¹, reference interval 6.0–8.6). The cat was given 1 unit of packed red blood cells and was re-evaluated by the oncology service 1 week later. The owner reported that the patient continued to have a very poor appetite and was extremely lethargic. The cat had a mild tachycardia (heart rate 160 min⁻¹), pale mucous membranes, grade II/VI systolic heart murmur and the mass on the left tarsus. CBC abnormalities included normocytic, normochromic anaemia (hematocrit 13.9%, reference interval 31.7–48.0) and thrombocytopenia (73.8 K μL⁻¹, reference interval 175–500). Blood leucocyte count was 7.44 K μL⁻¹ (reference interval 4.0–18.7), and there were 5550 neutrophils μL⁻¹ (reference interval 2300–14000). The absolute blood lymphocyte count was 1702 cells μL⁻¹ (reference interval 800–6100), and the majority of the lymphocytes were identified as plasmacytoid small lymphocytes or plasmacytoid lymphoblasts. Doxorubicin (Bedford Laboratories, Bedford, OH, USA) (1 mg kg⁻¹ intravenous) was given, and prednisone was increased to 1 mg kg⁻¹ every 12 h. Melphalan was discontinued.

Improvement was noted in the patient for 3 weeks, with an increase in appetite and physical activity. However, by the end of 3 weeks, the cat demonstrated anorexia, lethargy and vomiting. Abnormalities in physical examination included tachycardia (heart rate 260 min⁻¹), pale pink mucous membranes, grade II/VI systolic heart murmur and the mass on the left tarsus. The cat’s body weight was 6.0 kg. Haematology results revealed a normal leucocyte count (8.17 K μL⁻¹, reference interval 4.00–18.7), normal neutrophil count (4.54 K μL⁻¹, reference interval 2.3–14.0), but normocytic, normochromic anaemia (hematocrit 11.0%, reference interval 31.7–48.0), and thrombocytopenia (57.8 K μL⁻¹, reference interval 175–500). Sixteen per cent (1307 cells μL⁻¹) of all WBC were neoplastic plasma cells. Serum chemistry revealed an elevated creatinine concentration (2.5 mg dL⁻¹, reference interval 1.0–2.0), hyperphosphataemia (6.8 mg dL⁻¹, reference interval 3.0–6.6), hypercalcaemia (13.0 mg dL⁻¹, reference interval 9.1–11.2), hypernatraemia (161 mmol L⁻¹, reference interval 146–157) and hyperkalaemia (5.3 mmol L⁻¹, reference interval 3.5–4.8). Concern over potential renal insufficiency prompted change in chemotherapy to l-asparaginase (Elspar, Merck, Whitehouse Station, NJ, USA) (400 IU kg⁻¹ subcutaneous) and lomustine (CeeNU, Bristol-Myers Squibb, Princeton, NJ, USA) (60 mg m⁻² PO). One unit of packed red blood cells was transfused, and the cat was discharged. Owing to continued deterioration in the patient’s condition, the cat was euthanized 1 week later. A necropsy was not performed.

**Discussion**

Most of the veterinary literature regarding plasma-cell neoplasia in cats is limited to case reports (Carothers et al., 1989; Forrester et al., 1992; Larsen & Carpenter, 1994; Mandel & Esplin, 1994; Eastman, 1996; Sheafor et al., 1996; Weber & Tebeau, 1998; Zikes et al., 1998; Bienzle et al., 2000; Hickford et al., 2000). One case report described a cat with hepatic plasmacytoma and...
biclonal gammopathy; however, no evidence of bone marrow involvement was detected at necropsy examination (Larsen & Carpenter, 1994). Another case report documented extramedullary plasmacytoma with monoclonal gammopathy and Ig-associated amyloidosis, although the cat had normal bone marrow cytology at the time of necropsy examination. Also, the monoclonal gammopathy resolved after prednisone, melphalan and nandrolone decanoate chemotherapy (Carothers et al., 1989). Another report described a cat with retroperitoneal extramedullary plasmacytoma and a monoclonal gammopathy that resolved after surgical excision of the mass (Mandel & Esplin, 1994). Bone marrow evaluation did not reveal any neoplastic cells. On subsequent necropsy examination, serum protein electrophoresis and bone marrow evaluation did not definitively diagnose MM. A fourth case report involved a cat with a cutaneous plasmacytoma and osteolytic lesions, but monoclonal gammopathy was not identified (Eastman, 1996). There was evidence of metastasis of plasma-cell tumours at necropsy examination, but a diagnosis of MM was not established.

The case presented here illustrates some common points for patients suffering from MM. This patient was ultimately diagnosed with MM by virtue of a monoclonal gammopathy and Bence Jones proteinuria, two common findings in MM (Matus & Leifer, 1985; Bienzle et al., 2000). Also, when the patient ultimately became symptomatic for MM, the signs were non-specific (lethargy, anorexia and weight loss). These signs have been cited in previous case reports as the most common presenting complaints in patients diagnosed with MM (Drazner, 1982; Forrester et al., 1992; Sheafor et al., 1996; Hickford et al., 2000).

Previous case reports differ from the one described here in that none had documented evidence of a localized extramedullary plasmacytoma progressing to MM. The cat in this case could not be diagnosed with MM at initial examination with serum electrophoresis, radiographs and bone marrow cytology. Progression of disease in this cat was established several months later based on the presence of Bence Jones proteinuria and monoclonal gammopathy, which satisfies the requirement of at least two of the four previously discussed criteria for a diagnosis of MM. The authors also suspect that the bone marrow was infiltrated with plasma cells because the blood leucocytes were more than 50% atypical plasma cells and the patient was pancytopenic. Although cats frequently have soft-tissue involvement at the time of diagnosis of MM, to the authors’ knowledge, the documented progression of a local tumour to systemic disease in a cat has not been previously shown. The evolution of an extramedullary plasmacytoma into MM in this case is unusual. In dogs, it is known that a solitary osseous plasmacytoma may develop into systemic myelomatosis; however, cutaneous plasmacytomas are not considered to be highly metastatic (Vail, 2001). One case report exists of a dog with a cutaneous extramedullary plasmacytoma that progressed to MM (Lester & Mesfin, 1980), and the case reported here appears to be unique for cats. The high histopathologic grade of the tumour described here may account for the progression as this type of plasmacytoma may be more aggressive, but one previous study was unable to correlate tumour cell morphology to a prognostically relevant grading scheme (Platz et al., 1999). Furthermore, the patient described here had an IgA gammopathy that is another unusual feature; IgG is the Ig isotype found in most cats with MM (Jacobs, 1994; Bienzle et al., 2000).

Hypercalcaemia is common in humans and dogs with MM but has been rarely reported in cats (Sheafor et al., 1996). Proposed mechanisms of hypercalcaemia in MM include increased production of osteoclast-activating factors by neoplastic cells (MacEwen & Hurvitz, 1977; Drazner, 1982; Sheafor et al., 1996; Bienzle et al., 2000) and direct osteolysis (Sheafor et al., 1996). Binding of calcium by myeloma proteins has been proposed as another cause of hypercalcaemia; however, serum-ionized calcium should be normal in this circumstance (MacEwen & Hurvitz, 1977; Matus & Leifer, 1985; Dorfman & Dimski, 1992; Sheafor et al., 1996). The increased secretion of osteoclast-activating factors may be responsible for osteolytic lesions that are observed in MM (MacEwen & Hurvitz, 1977; Drazner, 1982). Renal disease has also been implicated as a cause of hypercalcaemia; however, serum-ionized calcium should be normal to decreased in this circumstance (Sheafor et al.,
Ionized calcium was measured in this patient at presentation to the emergency service (1.35 mmol L\(^{-1}\), reference interval 1.13–1.33). The mildly elevated ionized calcium concentration suggests that the increased total calcium may have been due to a paraneoplastic syndrome.

Because MM is a rare disorder in cats, the efficacy of treatment has been difficult to evaluate. Recommended treatment is melphalan at 2 mg m\(^{-2}\) orally once a day for 10 days, then every other day or, alternatively, 7 mg m\(^{-2}\) orally once a day for 5 days (Weber & Tebeau, 1998). Melphalan is used in combination with prednisone, 20 mg m\(^{-2}\) orally once a day for 10 days, then every other day or, alternatively, 5 mg once a day continuously. Clinical response is judged on the basis of reduction of Bence Jones proteinuria and the serum monoclonal globulin spike and alleviation of haemogram abnormalities (anaemia, thrombocytopenia and leukopenia). A decrease in Bence Jones proteinuria is often the first sign of improvement, although reduction of M-proteins may take 1–2 months (MacEwen & Hurvitz, 1977; Drazner, 1982). In dogs, the response rate is 92% for partial or complete remission and the median survival time is 540 days (Weber & Tebeau, 1998). In human patients, approximately 50% respond with a median survival time of over 2 years (Weber & Tebeau, 1998). In the cat described here, based on decreasing total protein and globulin concentrations and an increase in the neutrophil count, initial treatment with melphalan and prednisone appeared efficacious. Treatment response, however, was transient as the blood dyscrasias returned and signs reappeared within 2.5 months.

There are some limitations with the information presented in this case report. First, urine was not submitted at the time of first examination for Bence Jones protein analysis. It is possible to have light-chain proteinuria despite normal serum protein electrophoresis (Hoenig & O’Brien, 1988; King et al., 2002). There is also the possibility that malignant plasma cells existed in the bone marrow and that the first sample of bone marrow was obtained from an area that was not infiltrated by plasma cells. Indolent myeloma may be an explanation for this phenomenon, but clinical diagnosis of this phenomenon is difficult. It is also possible to have abnormal Ig production in the setting of normal gamma serum protein levels (Kyle, 1975).

Another limitation was the delay of clinical staging. Four months passed after the plasmacytoma was diagnosed prior to the patient being examined by an oncologist, and another month passed before abdominal ultrasound examination was performed. It is impossible to know the status of the iliac lymph node at the time of initial presentation. Haemogram and serum chemistry results were available for that time period and were normal, suggesting progression of the disease over a 6-month period. It is the authors’ clinical impression that this cat did not have MM at the time of the initial staging because it survived for 6 months without treatment.

Plasma-cell leukaemia is a disease with clinical features similar to MM (Bernasconi et al., 1989). It is also a malignant proliferation of plasma cells where greater than 20% of the differential leucocyte count or an absolute count of greater than 2 \(\times\) 10\(^{9}\) cells L\(^{-1}\) in blood are plasma cells (Bernasconi et al., 1989). The cat described here satisfied this criterion. However, plasma-cell leukaemia typically involves the visceral organs, progresses rapidly and has a much poorer prognosis when compared with MM (Couto et al., 1984; Bernasconi et al., 1989). There has only been one case of plasma-cell leukaemia reported in the veterinary literature and that was in a dog (Couto et al., 1984). The cat described here did not have organomegaly on radiograph or ultrasound examinations, and it survived for 4 months after the plasmacytosis was noted, which is atypical of plasma-cell leukaemia.

In the authors’ opinion, the veterinary literature suggests cats with plasmacytomas may develop myelomatosis, yet no true documentation of the phenomenon exists. This report describes a cat that developed MM from a localized extramedullary tumour. It is possible that this progression is not uncommon. We suspect that cases of feline plasma-cell neoplasia may not be diagnosed at an early stage because of non-specific clinical signs, variability in the course of clinical disease and inconsistencies in results of diagnostic tests used to diagnose MM. A greater understanding of this syndrome is necessary in order to determine the most appropriate therapy and long-term prognosis.
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References


