Multiple myeloma in a dog with biclonal gammopathy

Multipel myeloom bij een hond met biklonale gammopathie

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ABSTRACT

Multiple myeloma is an uncommon malignant neoplastic disease in humans and domestic animals associated with the excessive production of immunoglobulins by proliferated plasma cells. In this article, the findings associated with this disease in an eleven-year-old castrated beagle are described. Clinically, the dog had a reduced appetite, periodic vomiting, apathy and muscular tremors. Laboratory examinations revealed biclonal hypergammaglobulinemia, hypercalcemia, leucopenia, anemia, increased kidney and liver parameters and hyperproteinemia. Multiple myeloma was diagnosed by cytology from a fine-needle-bone-marrow aspirate. Treatment was initially successful, but relapse occurred. The dog was euthanized about ten weeks after diagnosis.

SAMENVATTING

Multipel myeloom is een zeldzaam maligne neoplastisch proces dat bij mens en dier kan voorkomen, geassocieerd met een overmatige productie van immunoglobulinen door prolifererende plasmacellen. In deze casuïstiek worden de bevindingen beschreven geassocieerd met deze aandoening bij een elf jaar oude, gecastreerde beagle. Klinisch vertoonde de hond verminderde appetijt, periodisch braken, apathie en spiertremor. De laboresultaten waren biklonale hypergammaglobulinemie, hypercalcemie, leukopenie, anemie, verhoogde nier- en leverwaarden en hyperproteïnemie. De diagnose van multipel myeloom werd gesteld aan de hand van een beenmergpunctie. De behandeling was initieel succesvol, maar door een relaps werd de hond geëuthanaseerd ongeveer tien weken na de diagnose.

Myeloma-related disorders (MRDs) are clonal plasma cell neoplasms including multiple myeloma (MM), macroglobulinemia, extramedullary plasmacytoma, solitary osseous plasmacytoma and plasma cell leukemia (Reising et al., 2021). Multiple myeloma (MM) is the most important plasma cell disorder regarding incidence (8% of all canine hematopoietic tumors, but less than 1% of all canine malignant tumors) and severity (Valli et al., 2002; Khanna and Foskett, 2017; Vail, 2020). It arises when a plasma cell or immunoglobulin-producing B-lymphocyte precursor lineage transforms and proliferates to form a neoplastic population of similar cells. In most instances, this population is monoclonal, producing a single immunoglobulin, although biclonal and polyclonal myeloma-related disorders exist (Khanna and Foskett, 2017). MM-cells produce excessive amounts of immunoglobulin (antibodies) or a fraction of antibodies, called M-protein (the 'M' in 'M-protein' stands for monoclonal). The M-protein can be any class of immunoglobulin or a part of the molecule, called a light-chain (i.e. Bence Jones proteins) or heavy chain molecules (i. e. heavy chain disease). A wide array of pathologic abnormalities and related clinical syndromes can occur as a result of tumor infiltration of various organ systems, the presence of high levels of circulating M-proteins or a combination of both (Valli et al., 2002; Khanna and Foskett, 2017). Bones that are very active in the production of blood cells, are most affected by MM. These include the ends of the long bones of the limbs, back bones, ribs, pelvis and skull. About 25 to 66% of patients with MM have vis-

ible bone lesions (Valli et al., 2002; Khanna and Foskett, 2017). This condition may cause a generalized thinning of the bones (diffuse osteopenia) or round punched out lesions. Due to weakening of the bone, fractures may occur. Bleeding tendencies are seen in about 33% of dogs affected by MM (Khanna and Foskett, 2017). M-proteins can prevent platelets from functioning properly and interfere with clotting factors (Khanna and Foskett, 2017). Hyperviscosity syndrome is a condition in which blood gets thicker than normal due to excessive amounts of immunoglobulin in the blood. This can cause neurological signs, such as depression seizures, coma, dementia, ophthalmologic abnormalities, cardiac and renal abnormalities. This is noticed in about 20% of the dogs with MM (Khanna and Foskett, 2017). About 33 to 50% of cases of MM have kidney failure, which can be caused by high calcium levels, Bence Jones proteins, hyperviscosity syndrome, tumor infiltration into the kidneys and kidney infections due to immunosuppression (Khanna and Foskett, 2017). A high calcium level in the blood may be caused by the production of a substance that acts like parathyroid hormone. Destruction of the bone may also cause increased calcium to enter into the blood stream. Immune deficiency with resultant infections may be caused by displacement of normal cells from the bone marrow by the tumor cells (leaving no room for normal white and red blood cell precursors) (Khanna and Foskett, 2017). Recently however, a case of MM with primary erythrocytosis in a dog has been described (Ricci et al., 2021).

There are no proven causes of MM; however exposure to the agricultural industry, petroleum products and irradiation are risk factors in humans (Khanna and Foskett, 2017). The average age of dogs affected by MM is eight to nine years; German shepherds are more commonly affected than other breeds. There is no sex predilection (Khanna and Foskett, 2017). Clinical signs in decreasing frequency include lethargy/weakness, lameness, coagulation disorders, ocular problems (hyphema, retinal detachment, blindness), increased thirst and polyuria and neurological signs (Khanna and Foskett, 2017). Many other nonspecific clinical signs may also be present, such as vomiting, weight-loss and malaise (Vail, 2020; Khanna and Foskett, 2017). Diagnosis of multiple myeloma in dogs requires the diagnosis of at least two of the following pathologies: lytic skeletal lesions, bone marrow plasmacytosis, Bence Jones proteinuria, or a monoclonal spike on serum protein electrophoresis (Johnson, 2012). Tests that are commonly used in patients that are suspected to have MM, include hematology and biochemistry, urinalysis, serum protein electrophoresis, urine testing for Bence Jones proteins, bone marrow biopsy, and X-rays of the bones. Treatment of MM is a treatment of the tumor itself and the secondary effects of the tumor. Chemotherapy never eradicates the entire tumor, but reduces the tumor burden significantly so that the patient feels well again. Radiation can be used to treat isolated plasma cell tumors. The median survival time in dogs with MM treated with chemotherapy (melphalan) is 540 days (Vail, 2020). In the present case, the diagnosis of MM with biclonal gammopathy, treatment and follow-up is described.

CASE REPORT

An eleven-year-old, castrated beagle of 14 kg was presented to the local veterinarian with reduced appetite, periodic vomiting and apathy. The animal lost 3 kg of body weight within six weeks. General examination revealed no remarkable abnormalities except the presence of muscular tremors. Initially, there was suspicion of a foreign object in the gastro-intestinal tract. X-rays with barium however revealed the absence of a corpus alienum; no abnormalities were observed at the bones present on the X-rays. In-house blood analysis at the veterinary practice was unsuccessful due to high viscosity of the collected blood sample. Ultrasound examination revealed a slightly enlarged liver, and severely enlarged spleen. Blood analysis at Medlab Bruyland revealed mild microcytic, hypochromic anemia, leukopenia (Sysmex XN-1000vet), increased kidney and liver function biomarkers, hypercalcemia, and hyperproteinemia (Roche Cobas 8000) with biclonal gammopathy (Sebia Capillarys 3 octa) (Table 1) (Figure 1A). Hypercalcemia was confirmed by measuring ionized calcium. A blood smear revealed the presence of blastic cells in the circulation (Figure 2).

Cytological examination of bone marrow revealed the absence of normal marrow hematopoietic cells, a relatively cell poor sample, in particular of the erythroid lineage. Proportionally, there were a lot of round cells (>5%) with pale to moderately basophilic cytoplasm, an eccentric, round nucleus and a clear perinuclear region representing the Golgi apparatus, clumped chromatin compatible with plasma cells (Figure 3). An Idexx snap 4dx including *Anaplasma*, *Ehrlichia*, *Dirofilaria* and *Borrelia*; and an Idexx snap *Leishmania* test were negative. The diagnosis of multiple myeloma in this dog was based on hyperglobulinemia with biclonal gammopathy on serum protein electrophoresis and bone marrow plasmacytosis. The dog was treated with cortisone (Dermipred® (prednisolone), CEVA, Belgium; 1mg/kg/10 days followed by 0.5mg/kg); Alkeran® (melphalan, Aspen, the Netherlands; 0.1mg/kg/ for 10 days, followed by 0.05mg/kg for 10 days), and Delursan® (Ursodeoxycholic acid, Patheon, France; 15mg/kg/day).

After three weeks of treatment, the dog was doing relatively well. He was active, more alert, gained some weight and did not express side effects of the treatment or anorexia. Blood analysis and serum electrophoresis revealed moderate microcytic, hypochromic anemia, improved renal and liver function biomarkers (except alkaline phosphatase (AP)), normal

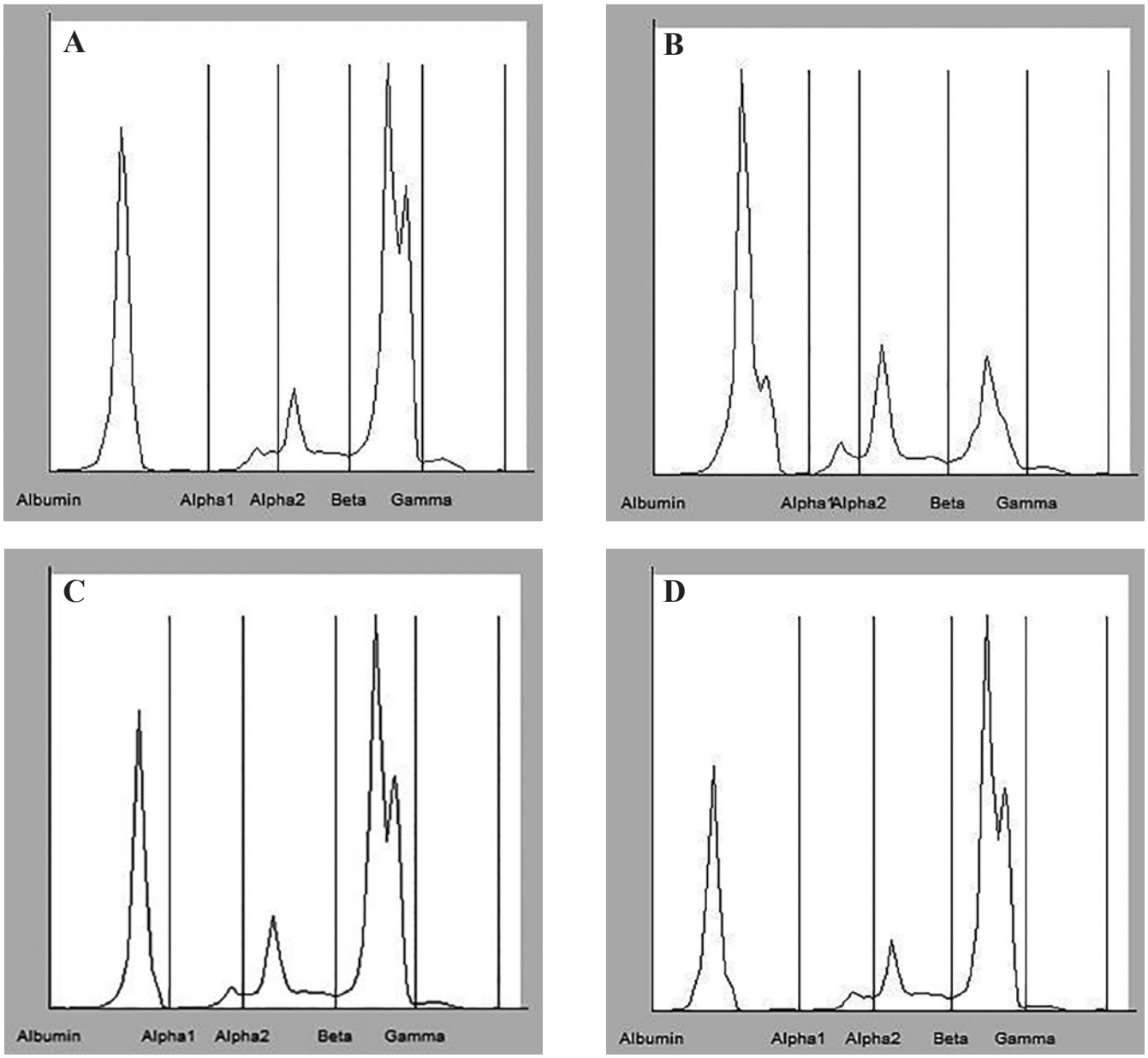

Figure 1. Serum protein electrophoresis (SPE) at diagnosis, after three weeks, seven weeks and ten weeks. A. SPE at diagnosis. The height and width of the peaks on the SPE are directly related to the number of proteins in each region and to the quantity of these proteins (Perret, 1999). Large biclonal gammopathy of the beta-globulines is shown. B. SPE after three weeks. The biclonal gammopathy has almost completely disappeared after three weeks of treatment. C. SPE after seven weeks. The biclonal peak is back, similar to the situation seven weeks earlier, due the modified treatment scheme. D. SPE after ten weeks. Similar plot as at the moment of diagnosis and as the one after seven weeks of treatment.

calcium, total protein and serum protein electrophoresis (Table 1) (Figure 1B). Due to the negative effect of the treatment on the erythrocytes, and the positive effect on the calcium, protein and serum protein electrophoresis, the melphalan and cortisone protocol was modified to every other day. However, blood analysis after another four weeks (i.e. seven weeks after the diagnosis and start therapy) revealed almost similar results as the initial blood analysis (Table 1) (Figure 1C). The dog had lost another kg of body weight, but was still doing relatively fine. The dog's general condition ten weeks after diagnosis deteriorated (with episodes of diarrhea, apathy and anorexia) and blood examination showed pancytopenia of the blood cells, and similar biochemistry results like the previous checkup (Table 1) (Figure 1D). As there had already been signs of iron deficiency anemia (microcytic, hypochromic anemia) at the moment of presentation and as severe iron deficiency was still noticed later, iron values were also evaluated during the routine blood examination.

Since the therapy with melphalan did not yield the expected results, it was decided in consultation with the owner to euthanize the dog. Further analyses, such as necropsy, were not allowed by the owner.

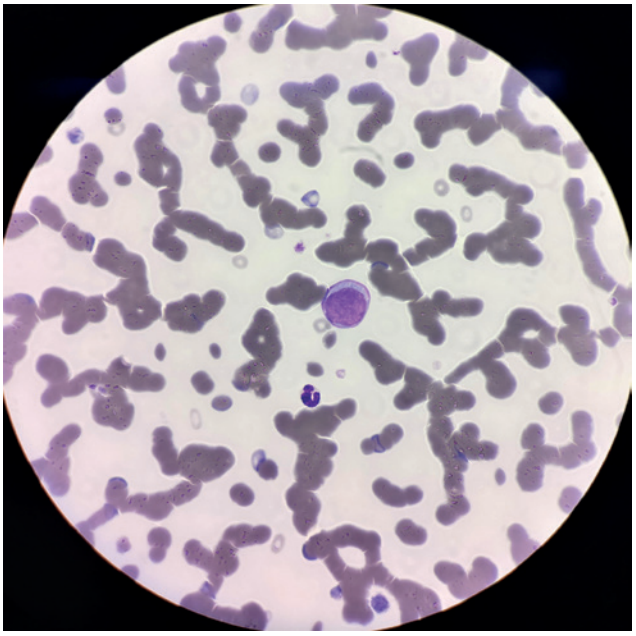

Figure 2. Blood smear with a large atypical lymphoid/plasmacytoid cell in the center. Several of these cells were found and could be part of the tumor disease. Magnification: 1000x - Wright-Giemsa stain.

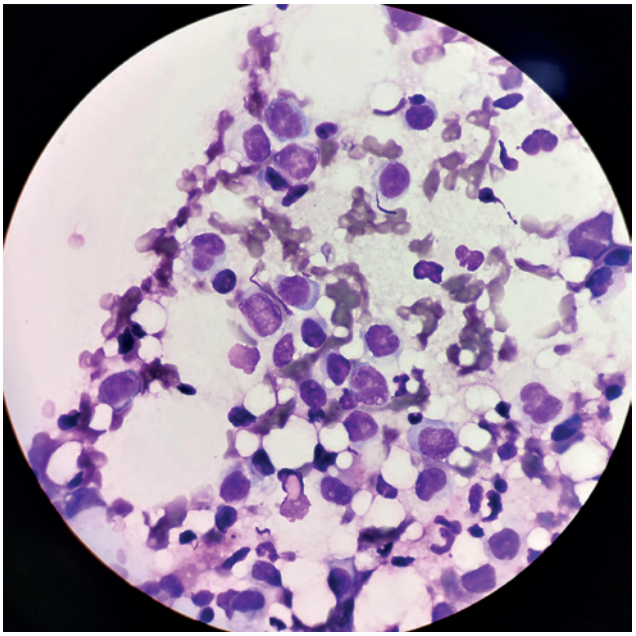

Figure 3. Cytology of bone marrow revealed the absence of normal marrow hematopoietic cells, especially of the erythroid lineage. Proportionally, there were a lot of round cells with pale to moderately basophilic cytoplasm, sometimes an eccentric, round nucleus and with a clear perinuclear region representing the Golgi apparatus, clumped chromatin, compatible with plasma cells. Magnification: 1000x - Hemacolor® Rapid stain.

DISCUSSION

Multiple myeloma is a systemic proliferation of malignant plasma cells or their precursors, typically originating from the bone marrow. Neoplastic cells can metastasize widely; in the present case, most likely in the spleen. The malignant transformation of a single plasma cell can secrete a single immunoglobulin, which often appears as a sharp, well-defined peak or gammopathy on serum protein electrophoresis (SPE). Diagnosing multiple myeloma in dogs requires the demonstration of at least two of the following criteria: bone marrow plasmacytosis, presence of osteolytic bone lesions, monoclonal hyperglobulinemia, and Bence-Jones proteinuria. In the present case, the diagnosis was based on biclonal hyperglobulinemia, hypercalcemia and plasma cell neoplasia in bone marrow. Lytic bone lesions were not observed in the present case. A Bence-Jones proteinuria analysis was not performed.

Serum protein electrophoresis (SPE) is an important tool in the work-up of multiple myeloma, as it is necessary for the identification of monoclonal gammopathy. SPE separates serum proteins based on their size, shape and electrical charge. It is often used in dogs to investigate the cause of increased total globulin concentration (McCudden et al., 2008). A dog with monoclonal gammopathy has a narrow-based peak in either the beta- or gamma region that is at least as high as the albumin peak (Perret, 1999; Facchini et al., 2010). It is determined 'monoclonal peak' because it is composed of a large quantity of immunoglobulin being produced by a single clone of neoplastic plasma cells. Multiple myeloma is the most common cause of a monoclonal gammopathy. B-cell lymphoma, lymphocytic leukemia and extramedullary plasmacytoma can also produce monoclonal gammopathy (Vail, 2020). Solitary osseous plasmacytoma and extramedullary plasmacytomas are rarely associated with monoclonal gammopathy (Meis et al., 1987; Adelman et al., 2014; Reising et al., 2021). Chronic infectious and inflammatory diseases however can also cause increases in immunoglobulin concentrations, although these conditions usually produce polyclonal gammopathies (wide-based with several peaks on the SPE) (Vail, 2020). In dogs, ehrlichiosis and visceral leishmaniasis, chronic pyoderma and several immune-mediated disorders have been reported in association with monoclonal gammopathy (Valli et al., 2002; Antognoni et al., 2010; Vail, 2020). Therefore, these diseases are important differentials in the absence of other diagnostic criteria for multiple myeloma (Valli et al., 2002; Antognoni et al., 2010). *Ehrlichia* and *Leishmania* tested negative in the present case and were therefore excluded in the differential diagnosis. Another less common SPE pattern observed in cases of multiple myeloma is biclonal gammopathy, as in the present case (Figure 1). Biclonal gammopathies have been rarely described in lymphoproliferative disorders in dogs (Facchini et al., 2010). In these cases, there are two separate clones of neoplastic cells, or a single clone of neoplastic cells produces two separate immunoglobulin isotypes, or the dimeric or multimeric forms of a single immunoglobulin are observed (Facchini et al., 2010).

Urine protein electrophoresis can also be used to detect Bence Jones proteinuria, which is present in 25-40% of dogs with multiple myeloma. Bence Jones proteins are the free immunoglobulin light chain components of the M-proteins. Since these light chains are relatively small, they can pass freely through the glomerular filtration barrier. In healthy dogs, any light chains that pass through the glomerular basement membrane are reabsorbed in the proximal tubules. However, with the magnitude of paraproteinemia that can be present in MM, the resorptive capacity of the proximal tubules is exceeded and the proteins enter the urine. Bence Jones proteinuria was not tested in this case due to the commercially unavailability of this test in veterinary medicine.

Bone marrow plasmacytosis is defined as a condition, in which plasma cells should at least be 20% of the total nucleated cell population in canine bone marrow aspirates (Vail, 2020), devoiding the normal hematopoietic cells (Valli et al., 2002). The standard number of plasma cells in bone marrow should not exceed 5%. In the present case, more than 20% of plasma cell-like tumor cells were present and the erythroid lineage was hypoplastic (Figure 3).

Table 1. Consecutive blood analyses with deviating values.

Hematology	**Day 1**	**After 3 weeks**	**After 7 weeks**	**After 10 weeks**		
Erythrocytes	6.61	3.89	5.71	5.36	10^6/µl	5.50-7.50
Hemoglobin	6.7	4	5.5	4.8	nmol/l	8.5-12.0
Hematocrit	36.4	22.5	31.7	27.1	%	42-54
MCV	55	58	56	51	fl	67-80
MCH	16	17	16	15	Pg	21-26
MCHC	30	28	28	29	g/dl	32-37
Thrombocytes	104	80	130	33	10^3/µl	200-400
	Giant platelets Platelet clots	**Giant platelets Plattelot clots**	**Platelet clots**			
Leukocytes	2.63	8.66	9.79	5.23	10^3/µl	6.00-12.00
Neutrophils	1.860	7.1	8.73	4.200	10^3/µl	3.20-11.80
Lymphoblasts	0.053		0.195	0.261		
Lymphocytes	0.528	0.9653	0..303	0.382	10^3/µl	1.00-4.80
Monocytes	0.180	0.61	0.548	0.408	10^3/µl	0.05-1.24
Eosinophils	0.000	0	0	0.020	10^3/µl	0.05-1.18
Basophils	0.010	0	0.010	0.010	10^3/µl	<0.100
Biochemistry						
Urea	15.47	8.18	9.36	6.31	mmol/l	2.00-6.70
Creatinine	149	76	92	96	µmol/l	70+1 kg LG
AST	72	42	70	75	U/l	<40
ALT	223	156	99	148	U/l	<60
gammaGT	<3	<3	<3	/	U/l	<15
AP	642	1617	820	878	U/l	10-50
Lipase	137	240	193	246	U/l	<125
Bile acids	4.6	12.1	12.8	8.8	µmol/l	<25
Ca	4.06	2.31	3.48	3.61	mmol/l	2.1-3.00
Ca ion	65.13		52.83	55.92	mg/l	40-52
Fe				5.3	µmol/l	16.3-37
Total protein	96.0	65.3	100	98.2	g/l	58.0-75.0
Albumin	32.7	38.9	32.7	28.8	g/l	28.0-38.0
Electrophoresis						
Albumin	30.3	53.8	27.2	26.1	%	43.0-54.0
Alpha 1	3.4	4.5	2.8	3.3	%	4.0-8.0
Alpha 2	10.8	19.4	14.0	12.1	%	12.0-22.0
Beta	53.5	20.7	54.8	57.3	%	15.0-23.0
Gamma	2.0	1.6	1.2	1.2	%	6.0-13.0
Albumin	29.1	35.1	27.2	25.6	g/l	28.0-38.0
Alpha 1	3.3	2.9	2.8	3.2	g/l	3.0-6.0
Alpha 2	10.4	12.7	14.0	11.9	g/l	6.0-14.0
Beta	51.4	13.5	54.8	56.3	g/l	10.0-14.0
Gamma	1.9	1.0	1.2	1.2	g/l	3.0-8.0

Black: within reference interval; Blue: lower than reference interval; Red: higher than reference interval.

Hypercalcemia can be malignancy-associated (e.g. lymphoma, multiple myeloma, apocrine gland carcinoma of the anal sac, primary or metastatic bone neoplasia). It can be caused by hypoadrenocorticism, primary hyperparathyroidism, granulomatous diseases, hypervitaminosis D and renal failure. In this dog, the hypercalcemia was most likely malignancy-associated, although PTHrp and osteoclast activating factors were not measured. Hypercalcemia occurs in approximately 10% of the MM cases. Concurrent hypercalcemia in dogs with MM indicates a worse prognosis, as well as osteolytic bone lesions and Bence-Jones proteinuria (Matus et al., 1986). In the present case, the hypercalcemia may have interfered with the prognosis (i.e. limited survival time).

Anemia in multiple myeloma patients is due to chronic disease, hemorrhage due to coagulopathy, myelophthisis and red blood cell destruction. Normocytic, normochromic, nonregenerative anemia is one of the most common findings on complete blood count (CBC); two-thirds of dogs and cats with MM are affected (Matus et al., 1986; Patel et al., 2005; Hanna, 2005; Mellor et al., 2006). In the present case however, microcytic, hypochromic anemia was observed. Erythrophagocytic multiple myeloma has been reported in a cat, dogs and humans, so it may be a source of anemia as well (Webb et al., 2008; Hom and Olsen, 1984). Pancytopenia may be seen in patients with marked bone marrow infiltration with neoplastic cells, like in the present case. Extensive bone marrow involvement with malignant cells can theoretically result in decreased capacity for functional erythropoiesis or other blood cell types (i.e. leucocytes and platelets). In addition, production of erythropoietin in the presence of myeloma-associated renal insufficiency is depressed (Vanderwall et al., 2013). An additional mechanism of anemia may be a shortened survival of RBC precursors due to the expression of a ligand on the surface of the malignant plasma cells, which may cause apoptosis of erythroid precursors within the marrow (Silvestris et al., 2002). These mechanisms may contribute to myeloma-associated anemia.

The almost universal occurrence of anemia in myeloma patients is due to hypoferremia and the decreased availability of iron for the developing erythrocyte. The availability of iron for the developing erythrocytes is depressed, resulting in microcytic, hypochromic anemia (Vanderwall et al., 2013), like in the present case. Iron studies demonstrated low to normal serum iron levels (Ludwig et al., 2004). Bone marrow biopsy may show an increase in hemosiderin-laden macrophages with normal to increased iron stores. This is consistent with impaired iron mobilization and release (Ludwig et al., 2004). Iron utilization is impaired due to increased pro-inflammatory cytokines that stimulate the production of the iron-regulatory hormone hepcidin in the liver (Rivera et al., 2005). Hepcidin is the primary negative regulator of iron transport and iron release from erythrocyte-recycling macrophages and enterocytes (Rivera et al., 2005). Thus, ingested iron taken up by enterocytes cannot be released into the circulation and is lost as enterocytes are sloughed into the lumen of the GI tract. Likewise, iron catabolized from old RBCs, obtained from hemoglobin degradation, cannot be released for re-utilization. The end-result is hypoferremia, depressed iron delivery to developing erythrocytes, diminished hemoglobin synthesis and anemia (Ganz, 2006). When anti-MM therapy is successful, this mechanism stops, resulting in increased iron availability to erythropoietic cells (Vanderwall et al., 2013), which was not observed in the present case.

The treatment protocol for MM is based on melphalan (Matus et al.,1986; Fernandez and Chon, 2018; Vail, 2020). This is an alkylating agent, which limits cell division. It should be administered orally on a daily basis. Additionally, prednisone, a steroid, increases the efficacy of melphalan and has an antihypercalcemic effect. It is typically discontinued after two months of treatment. Other alkylating agents that can be used to treat MM are cyclophosphamide (instead of melphalan or in combination with melphalan) and chlorambucil (Fernandez and Chon, 2018). Before and during treatment, blood tests are necessary to evaluate the immune system function, as well as the medication's effect on kidney and liver. Side-effects in treated dogs are generally reversible and disappear after treatment. Side-effects of melphalan most often develop in the gastrointestinal tract with more serious side-effects arising from bone marrow suppression (Fernandez and Chon, 2018). In the present case, the first three weeks of treatment had a negative effect on the erythroid lineage, but a positive effect on the biochemistry parameters. Changing the melphalan treatment protocol hereafter, wiped out almost completely all the improvements of the biochemistry parameters, resulting is similar values as to the moment of diagnosis. Although the erythroid lineage showed moderate recovery after seven weeks, it eventually resulted in pancytopenia after ten weeks (Table 1).

A positive response to chemotherapy includes resolution of clinical signs. It may take three to four weeks to notice improvement of the bony lesions (based on radiographs) and reduction of the immunoglobulins in the blood and Bence Jones proteins in the urine (seen three to six weeks after induction of treatment) (Vail, 20201). A reduction of the biclonal gammopathy was also observed after three weeks in the present case, but reappeared after seven weeks due to alteration of the melphalan treatment protocol after three weeks and continued to be present at ten weeks after diagnosis.

In conclusion, MM is normally a well treatable condition since chemotherapy can greatly extend the quality and duration of life. The overall response rate for dogs treated with melphalan and prednisone is 92%, with 43.2% of dogs achieving a complete res-

ponse. The median survival time is about 540 days (Valli et al., 2002). However, full recovery cannot be expected and eventual relapse during therapy is likely. In the present case, MM complications like anemia/ pancytopenia interfered with the viability leading to euthanasia.

ACKNOWLEDGEMENTS

The authors would like to thank the staff of Medlab Bruyland for their assistance.

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