Case Report

jfms OPEN REPORTS

Journal of Feline Medicine and Surgery Open Reports
1–6

DOI: 10.1177/2055116917719209
journals.sagepub.com/home/jfmsopenreports

This paper was handled and processed by the European Editorial Office (ISFM) for publication in *JFMS Open Reports*

SAGE

Concomitant multiple myeloma and probable phaeochromocytoma in a cat

Mario Cervone

Abstract

Case summary Herein a drug-resistant IgG-lambda-type multiple myeloma associated with probable phaeochromocytoma in a cat is described. A 12-year-old cat presented with weakness, weight loss, progressive blindness and open-mouth breathing, in addition to polyuria and polydipsia of 2 months' duration. Abdominal ultrasonography revealed a left adrenal mass. Phaeochromocytoma was suspected on the basis of cytology and was associated with systemic hypertension. Biochemistry showed hyperproteinaemia. Serum protein electrophoresis revealed a narrow spike in the gamma region, identified as IgG lambda type at immunoelectrophoresis. Bone marrow cytology revealed an infiltrate with numerous mature plasma cells. The cat was resistant to two different drugs for multiple myeloma and was euthanased 6 months later because of anorexia and persistent poor general condition.

Relevance and novel information This is the first clinical description of multiple myeloma associated with a suspected phaeochromocytoma in a cat.

Accepted: 13 June 2017

Case description

A 12-year-old, male neutered domestic shorthair cat was admitted for polyuria and polydipsia of 2 months' duration, in addition to progressive blindness, weight loss, weakness and several episodes of open-mouth breathing. Initial physical examination findings included a temperature of 38.7°C, pale mucous membranes and a body condition score of 3/9 (according to World Small Animal Veterinary Association Global Nutrition Committee criteria).

Complete ocular examination revealed inconsistent menace response and bilateral focal areas of retinal detachment, haemorrhage and oedema. On auscultation, a cardiac gallop rhythm was detected, associated with an increased respiratory rate and normal breathing sounds. Systolic arterial blood pressure (SAP) measured by the Doppler method was repeatedly high (mean 280 mmHg; three measurements performed daily on four separate days). Urinalysis (specific gravity, urinary dipstick and urinary sediment examination) revealed a urine specific gravity of 1.020, without further abnormalities. The urinary protein:creatinine ratio was 0.2. Complete blood count (CBC) and biochemistry results are summarised in Table 1. CBC values revealed mild, non-regenerative anaemia (haematocrit 28%; reference interval [RI] 30–45%). Biochemistry revealed hyperproteinaemia (97 g/l; RI 60–80 g/l), hypoalbuminaemia (23 g/l; RI 25–39 g/l) and hyperglobulinaemia of 74 g/l. Serum protein electrophoresis revealed a spike in the gamma region (47 g/l; RI 12–32 g/l) (Figure 1a). The appearance of this spike was suggestive of oligoclonal gammopathy. Serum agar gel immunodiffusion and immunoelectrophoresis identified the M-protein as monoclonal IgG lambda type (Figure 1b). To rule out potential infectious causes of monoclonal gammopathy, serological testing for feline leukaemia virus and feline immunodeficiency virus (SNAP FIV/FeLV Combo Test; IDEXX Laboratories) was undertaken. This was negative, as was indirect immunofluorescence for feline coronavirus and *Ehrlichia* species antibodies.

Three-view thoracic radiographs were unremarkable. Cardiac ultrasonography showed moderate asymmetric

Small Animal Veterinary Clinic, Marseille, France

Corresponding author:
Mario Cervone DVM, Small Animal Veterinary Clinic, 283 Chemin de Château-Gombert 13013 Marseille, France
Email: mariocervone@live.it

Table 1 Laboratory measurements at admission

Analyte (units)	Reference interval	Admission
WBCs ($\times 10^9$/l)	6.0–16.0	10.4
RBCs ($\times 10^{12}$/l)	5.0–10.0	4.8*
Haemoglobin (g/dl)	9.5–15.0	9.2*
Haematocrit (%)	30–45	28*
Sodium (mmol/l)	150–165	161
Potassium (mmol/l)	3.5–5.8	3.7
Chloride (mmol/l)	106–123	115
Ionised calcium (mmol/l)	1.13–1.38	1.14
Glucose (g/l)	0.7–1.6	1.2
Urea (g/l)	0.3–0.6	0.4
Creatinine (mg/l)	6.0–15.0	10
Total protein (g/l)	60–80	97*
Albumin (g/l)	25–39	23*
Globulins (g/l)	35–55	74*
ALP (UI/l)	5.0–50	37
ALT (UI/l)	19–100	21
Total T4 (nmol/l)	20–50	35
Free T3 (pmol/l)	<6	5

*Abnormal findings
WBCs = white blood cells; RBCs = red blood cells; ALP = alkaline phosphatase; ALT = alanine transaminase; T4 = thyroxine; T3 = triidothyronine

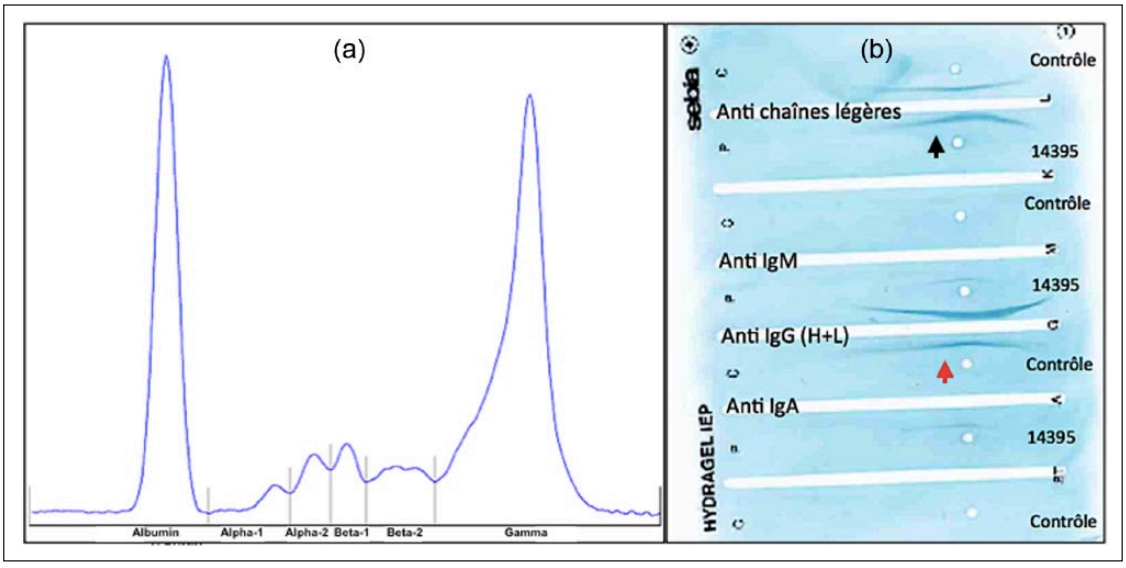

Figure 1 (a) Protein electrophoresis of serum indicating a narrow spike in the gamma region. (b) Immunoelectrophoresis (IEP) of serum protein showing a precipitin arc between the anti-IgG antibody and the serum (red arrow), and between anti-lambda chain and serum (black arrow). Châines légères = light chains

hypertrophy with subaortic remodelling and fibrosis, most probably due to increased SAP. Abdominal ultrasonography showed a left adrenal mass (Figure 2), without evidence of vascular invasion. The right adrenal gland was unremarkable. Low-dose dexamethasone suppression (0.1 mg/kg IV) and urine cortisol: creatinine ratio tests were performed to investigate the adrenal activity and a possible inappropriate secretion of hormones by the adrenal mass, but both were within the RIs. Several serum potassium concentrations were repeatedly within the RI and, consequently, excessive aldosterone production was not investigated. Cytological examination of the adrenal mass, obtained by ultrasound-guided fine-needle aspiration (FNA), revealed clusters of intact cells showing polygonal nuclei with prominent nucleoli, pale cytoplasm and fine, basophilic,

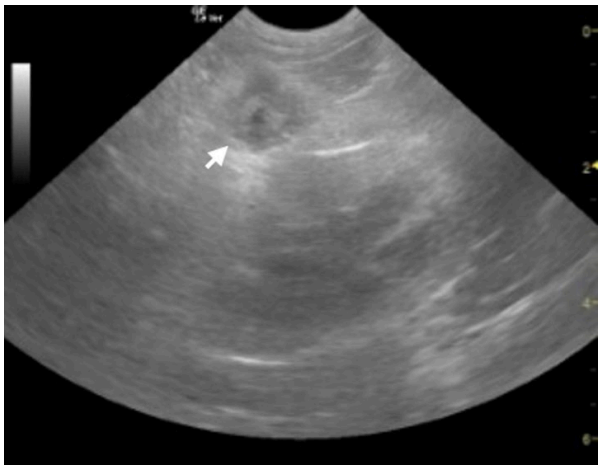

Figure 2 Ultrasound image of the left adrenal and adjacent kidney in long axis

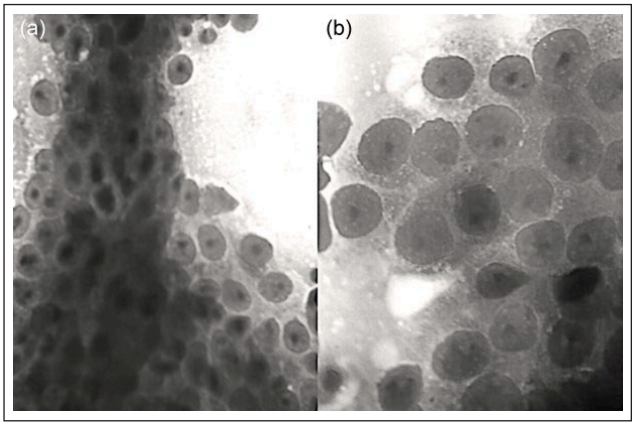

Figure 3 Cluster of intact cells from the adrenal mass: (a) × 10; (b) × 100. Cells show a high nuclear: cytoplasmic ratio, polygonal nuclei with prominent nucleoli, pale cytoplasm and fine intracytoplasmic granules

intracytoplasmic granules (Figure 3a,b). Furthermore, in order to investigate a potential haematopoietic neoplastic origin of the monoclonal gammopathy, a bone marrow aspirate from the right wing of the ilium was obtained under sedation using a Mallarmé trocar (18 G). Bone marrow cytology indicated an increased myeloid:erythroid ratio due to erythroid hypoplasia, associated with an increase in plasma cells (14%; RI <10%).[1] Plasma cells showed small mature-appearing nuclei and a large cytoplasm filled with one large Golgi apparatus (Figure 4). No malignant changes in the morphology of plasma cells were detected. To investigate a plasmacytic invasion of the spleen and liver, cytological samples were obtained by ultrasound-guided FNA, which revealed no abnormalities. PCR for *Leishmania infantum* and *Mycoplasma* species in both blood and bone marrow specimens were negative. Based on these

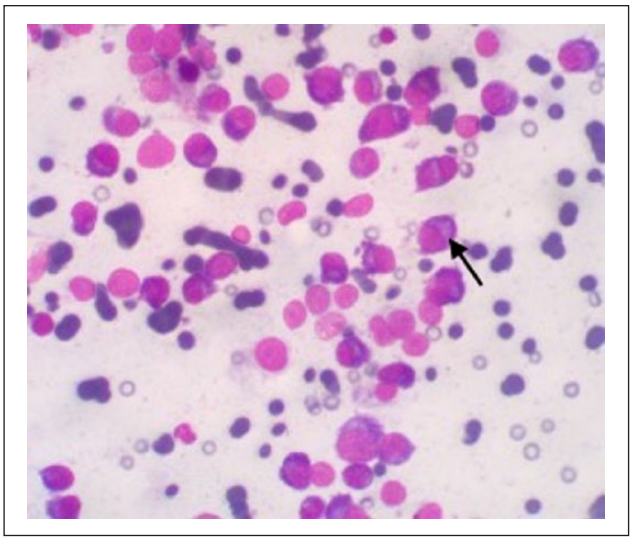

Figure 4 Bone marrow aspirate stained with May–Grünwald Giemsa, × 100. Numerous plasma cells containing a small mature-appearing nucleus and a large cytoplasm filled with one large Golgi apparatus (black arrow). *(Courtesy of Laboratoire Vebio; Arceuil, France)*

findings, a diagnosis of multiple myeloma (MM), associated with a probable phaeochromocytoma, was made.

Previous publications in human medicine have reported a bone marrow plasmacytic invasion induced by cytokines secreted by an adrenal mass, particularly interleukin (IL)-6.[2–4] Measurement of serum IL-6 concentration was not possible and adrenalectomy was declined by the owner. Therefore, immunocytochemistry using feline antibodies to IL-6 (R&D System) was performed on the cytological samples of the adrenal mass. Samples were divided into three different areas and counterstained with a 4',6-diamidino-2-phenylindole solution (ThermoFisher Scientific), according to the manufacturer's instructions. Reaction with feline antibodies to IL-6 was than observed in fluorescence microscopy and was compared with a negative control. Positive reactions of some adrenal cells to IL-6 antibodies were achieved only at a high antibody titre, which is not consistent with IL-6 secretion (Figure 5a,b).

The patient was initially treated (day 0) with a combination of prednisolone (2 mg/kg q24h) and melphalan (0.1 mg/kg q48h) by mouth, plus amlodipine (0.18 mg/kg) and spironolactone (2 mg/kg) by mouth for management of MM and systemic hypertension, respectively, but no improvement in clinical and biological condition was observed at days 10, 30 and 45. Therefore, a chemotherapy protocol with cyclophosphamide (200 mg/m² every week) by mouth plus prednisolone (2 mg/kg q24h) was undertaken, but once again no improvement was observed at days 55, 85 and 90. The cat was euthanased 6 months later owing to persistent poor general condition. Autopsy was declined by the owner.

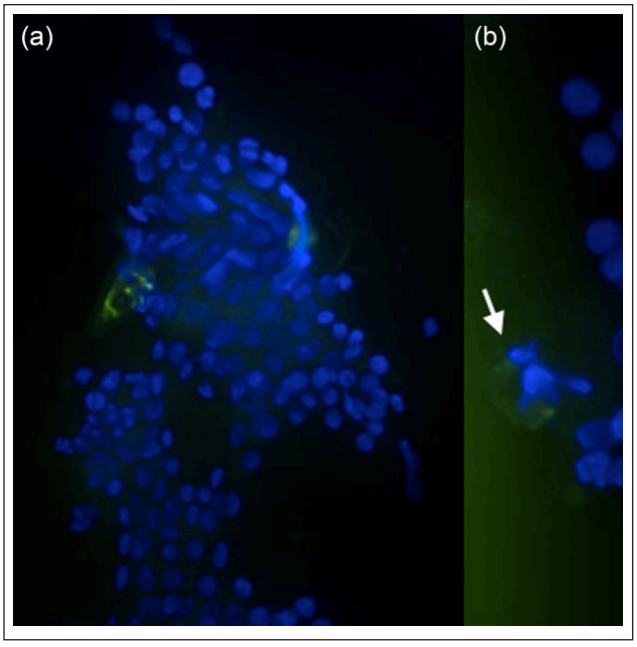

Figure 5 (a) Immunocytochemistry of the adrenal mass with feline antibodies to interleukin (IL)-6 (counterstained with a 4',6-diamidino-2-phenylindole solution, × 40). (b) Only focal positive reaction of the cytoplasm of tumour cells with feline antibodies to IL-6 are visible (coloured in green; white arrow). IL-6 secretion by tumour cells was consequently not confirmed

Discussion

The purpose of this case report is to document probable phaeochromocytoma and MM in a cat. Phaeochromocytomas are extremely rare tumours in domestic animals and to the best of the author's knowledge only eight cases of feline phaeochromocytoma are reported in the peer-reviewed literature.[5–7] Phaeochromocytomas are often malignant neoplasias, with a median survival time of 20 weeks.[7] Clinical signs are secondary to catecholamine-induced hypertension or due to the presence of a space-occupying mass, and include weakness, collapse, open-mouth breathing, muscle tremors, restlessness, and polydipsia and polyuria.[5,7] However, hypertension is not always demonstrated as catecholamine secretions may be paroxysmal.[7] Given the vague signs of phaeochromocytoma, an ante-mortem diagnosis is a clinical challenge. Furthermore, routine haematology, biochemistry and urinalysis are non-specific.[6]

In humans, biological diagnosis of a phaeochromocytoma is based on documenting abnormal regulation of catecholamines.[6] Thus, one of the initial tests performed in human medicine is direct measurement of catecholamines (eg, epinephrine) or catecholamine breakdown products (eg, metanephrines or urine vanillylmandelic acid) in the blood or urine via high-performance liquid chromatography. In veterinary medicine, a prospective study investigated plasma free metanephrine and normetanephrine levels in healthy cats, cats with non-adrenal disease and in a cat with a suspected phaeochromocytoma, demonstrating an elevated normetanephrine level in the latter.[5] However, a normetanephrine cut-off level to diagnose phaeochromocytoma in cats has not yet been developed and tests for phaeochromocytomas are not commercially available in veterinary medicine.[6] Nuclear imaging via nuclear scintigraphy or positron emission tomography can also be performed to achieve a preoperative diagnosis of phaeochromocytoma. Nuclear combines functional activity with anatomical localisation, allowing identification of the presence of metastasis and multifocal disease.[6] Unfortunately, this technique is not easily available in veterinary patients, and in this case the owner declined referral to a specialist centre in Paris (France). Finally, the catecholamine suppression test can also be performed in humans to diagnose phaeochromocytoma, but this test lacks sensitivity and specificity and has not been previously evaluated in domestic animals.[6]

Diagnosis of a phaeochromocytoma in animals requires demonstration of an adrenal mass. This is typically achieved with radiography, ultrasonography, CT or MRI.[6] Abdominal ultrasonography is recommended as part of the staging process in cats suspected of having a phaeochromocytoma, but it is neither sensitive nor specific.[5] Indeed, in a retrospective study of 33 feline adrenal masses, only three patients had phaeochromocytomas.[7]

In the current case, the diagnosis of adrenal phaeochromocytoma was suspected on the basis of a left adrenal mass at abdominal ultrasonography, associated with a chronic increase in SAP. Because hypertension is present in >70% of cats with an adrenal tumour,[7] further causes of a unilateral adrenal mass were considered in the differential diagnosis of this patient. In companion animals, adrenal tumours may be primary or metastatic, and arise from different areas of the adrenal gland.[8] Primary neoplastic proliferations of the adrenal cortex are classified as adrenal adenoma and adrenal carcinoma, depending on their biological behaviour, whereas adrenal medullary tumours are called phaeochromocytomas.[9] Furthermore, adrenal tumours may be functionally active, secreting inappropriate amounts of one or more hormones and causing tumour-related syndromes (eg, hyperadrenocorticism or hyperaldosteronism). In contrast, a variety of vague and non-specific clinical signs attributed to excessive secretion of catecholamines have been reported in patients with phaeochromocytomas.[4,9,10] In the current case, a hormone-secreting cortical adrenal neoplasia was ruled out on the basis of normal low-dose dexamethasone suppression tests and several normal serum potassium concentrations. Furthermore, a medullary

origin of the adrenal lesion was suspected on the basis of the cytological results of FNA. In the examined cat, the suspicion of phaeochromocytoma was strongly supported by the cytology of the mass. A recent study demonstrated that cytology in the characterisation of a primary adrenal mass is useful in discriminating cortical from medullary tumours and it may represent a rapid and easy method to correctly diagnose an adrenal tumour.[8] However, the risk of complications associated with FNA of an adrenal tumour should be considered. Indeed, potential severe and even fatal side effects (eg, pain, uncontrolled haemorrhage or severe hypertensive crisis) could arise from the sudden release of catecholamines, especially during FNA of phaeocromocytomas.[8]

MM is a rare multifocal plasma cell neoplasm involving bone marrow, with an estimated incidence of <1% of all feline haematopoietic neoplasms.[11] It is the most common cause of M-proteins, but other conditions can occasionally induce a monoclonal gammopathy in cats, such as chronic infection (leishmaniosis, ehrlichiosis, chronic pyoderma, feline infectious peritonitis), amyloidosis, B-cell lymphoma, Waldenström's macroglobulinaemia, monoclonal gammopathy of undetermined significance and bronchial carcinoma.[11,12] In the present cat, a diagnosis of a concomitant infectious disease was ruled out, as well as the presence of a primary or paraneoplastic monoclonal gammopathy. Furthermore, current published recommendations for determining a diagnosis of MM in animals require two of the following four criteria: (1) bone marrow plasmacytosis, (2) monoclonal gammopathy based on serum protein electrophoresis, (3) osteolysis and (4) light-chain (Bence-Jones) proteinuria.[12] The cat examined herein met two (bone marrow plasmacytosis and monoclonal gammopathy) of these criteria. Moreover, of the 27 published feline myeloma cases with immunoelectrophoresis results, 22 had IgG gammopathies, as described in the cat in the present report.[11,13]

In humans and dogs, an association between the presence of an adrenal phaeochromocytoma and concurrent neoplasia has been reported.[8] Concurrent neoplasia was found in >50% of the canine phaeochromocytoma cases in two large retrospective studies.[14,15] Interestingly, an association between MM and adrenal phaeochromocytoma has been previously reported in a jaguar (*Panthera onca*), associated with a cortical adenocarcinoma in the same gland.[16] A phaeochromocytoma can produce a variety of biologically active neuropeptides and hormones other than catecholamines. In recent years, increasing evidence indicates that this tumour also secretes cytokines, mainly IL-1, IL-6, tumour necrosis factor-alpha and interferon-γ.[2] IL-6 is a pleiotropic cytokine, originally cloned as a B-cell stimulatory factor, that is overexpressed in response to injury, inflammation and infection. Its role in cancer is complex, and autocrine and paracrine mechanisms are involved, including the promotion of the survival, migration and drug resistance of malignant plasma cells in MM.[12,17] Experimentally, deregulated expression of the IL-6 gene can trigger polyclonal plasmacytosis resulting in the generation of a malignant monoclonal plasmacytoma in mice.[18] Consistent with this theory, IL-6-deficient mice do not develop plasmacytoma, indicating the critical role played by IL-6 in murine plasmacytomagenesis.[19] In humans, IL-6 is physiologically expressed in the adrenal cortex, but not in the adrenal medulla and a number of clinical cases have reported the presence of IL-6-producing adrenal phaeochromocytoma.[2] Ectopic IL-6 production by phaeochromocytomas has been demonstrated by elevated serum levels of IL-6 or by immunohistochemical IL-6 expression on specimens of the resected adrenal tumours.[2–4] Furthermore, a fall in serum IL-6 levels after adrenalectomy has been reported.[2]

According to the finding of infiltrating mature plasma cells in the bone marrow of two human patients suffering an IL-6 producing pheochromocytoma,[18,20] it was hypothesised that the phaeochromocytoma in the examined cat may have supported the activation and survival of malignant plasmacytosis in bone marrow, via the secretion of IL-6. Moreover, high serum levels of IL-6 is one of the most common causes of drug-resistance in patients suffering from MM,[17] and it may explain the absence of clinical and biological improvement in the present cat after two different treatments for MM. Unfortunately, the serum concentration of IL-6 was not measured in the cat examined herein, and adrenal secretion was not confirmed by immunocytochemistry with feline antibodies against IL-6. The poor adrenal IL-6 secretion in the current case may be due to the inadequate pretreatment of cytological samples, such as a lack of storage at −20°C before immunocytochemistry, as recommended by the manufacturer.

Conclusions

To the best of the author's knowledge, this is the first clinical description of MM associated with a suspected phaeochromocytoma in a cat. Simultaneous neoplasms tend to be rare in feline patients,[13] and the information reported herein should alert veterinarians to being vigilant for multiple neoplastic processes in cats.

Acknowledgements The author would like to thank Laboratoire Vebio (Creteil, France) for assistance in the cytology evaluation of the bone marrow; Laboratoire LDH-Vet (ONIRIS Nantes, France) for the realisation of the immunoelectrophoresis; and Dr Nadine Martin-Garcia (INSERM-Creteil, France) for her assistance in the immunocytochemistry.

Conflict of interest The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding The authors received no financial support for the research, authorship, and/or publication of this article.

References

1 Morrison J and Dobson J. **Haematopoietic system**. In: Morrison J and Dobson J (eds). Small animal oncology. Oxford: Wiley-Blackwell, 2001, pp 228–251.

2 Minetto M, Dovio A, Ventura M, et al. **Interleukin-6 producing pheochromocytoma presenting with cute inflammatory syndrome**. *J Endocrinol Invest* 2003; 26: 453–457.

3 Kang JM, Lee WL, Kim WB, et al. **Systemic inflammatory syndrome and hepatic inflammatory cell infiltration caused by an interleukin-6 producing pheochromocytoma**. *Endocr J* 2005; 52: 193–198.

4 Yaman S, Soyluk O, Altunoglu E, et al. **Interleukin-6-producing pheochromocytoma presenting with fever of unknown origin**. *Clinics (San Paulo)* 2011; 66: 1834–1835.

5 Wimpole JA, Adagra CFM, Billson MF, et al. **Plasma free metanephrines in healthy cats, cats with non-adrenal disease and a cat with suspected phaeochromocytoma**. *J Feline Med Surg* 2010; 12: 435–440.

6 Calsyn JDR, Green RA, Davis GJ, et al. **Adrenal pheochromocytoma with contralateral adrenocortical adenoma in a cat**. *J Am Vet Med Assoc* 2010; 46: 36–42.

7 Daniel G, Mahony OW, Markovich JE, et al. **Clinical findings, diagnostics and outcome in 33 cats with adrenal neoplasia (2002–2013)**. *J Feline Med Surg* 2016; 18: 77–84.

8 Bertazzolo W, Didier M, Gelain ME, et al. **Accuracy of cytology in distinguishing adrenocortical tumors from pheochromocytoma in companion animals**. *Vet Clin Pathol* 2014; 43: 453–459.

9 Feldman EC and Nelson RW. Canine and feline endocrinology and reproduction. 3rd ed. Philadelphia, PA: Saunders, 2004.

10 Djajadiningrat-Laanen S, Galac S and Kooistra H. **Primary hyeraldosteronism: expanding the diagnostic net**. *J Feline Med Surg* 2011; 13: 641–650.

11 Patel RT, Caceres A, French AF, et al. **Multiple myeloma in 16 cats: a retrospective study**. *Vet Clin Pathol* 2005; 34: 341–352.

12 Cervone M and Beurlet S. **Primary bronchial carcinoma associated with bone marrow metastasis and paraneoplastic monoclonal gammopathy**. *JFMS Open Rep* 2016; 2: 1–5.

13 Bagwell JM, Herd HR, Breshears MA, et al. **Concurrent multiple myeloma and mast cell neoplasia in a 13-year-old castrated male Maine Coon cat**. *Vet Clin Pathol* 2017; 46: 151–157.

14 Gilson SD, Withrow SJ, Wheeler SL, et al. **Pheochromocytoma in 50 dogs**. *J Vet Intern Med* 1994; 8: 228–232.

15 Barthez PY, Marks SL, Woo J, et al. **Pheochromocytoma in dogs: 61 cases (1984–1995)**. *J Vet Intern Med* 1997; 11: 272–278.

16 Port CD, Maschgan ER, Pond J, et al. **Multiple neoplasia in a jaguar (*Panthera onca*)**. *J Comp Pathol* 1981; 91: 115–122.

17 Fairfield H, Falank C, Avery L, et al. **Multiple myeloma in the marrow: pathogenesis and treatment**. *Ann N Y Acad Sci* 2016; 1364: 32–51.

18 Hirano T. **Interleukin 6 (IL-6) and its receptor: their role in plasma cell neoplasias**. *Int J Cell Cloning* 1991; 9: 166–184.

19 Hishihara K and Hirano T. **IL-6 in autoimmune disease and chronic inflammatory proliferative disease**. *Cytokine Growth Factor Rev* 2002; 13: 357–368.

20 Moss RL. **Multiple myeloma with maxillary myelomatous epulis and malignant pheochromocytoma**. *Oral Surg Oral Med Oral Pathol* 1958; 11: 951–959.