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CASE REPORT
Peripheral neuropathy in a cat with renal lymphoma

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A 12-year-old male cat was referred for progressive limb weakness lasting 2 weeks. Physical examination detected muscle atrophy and bilateral renomegaly with distortion of the renal contours. The cat was ambulatory but tetraparetic. It showed a peculiar posture on forelimbs with bilateral flexion of the carpi and extrarotation of forearms. The cat was unable to go upstairs or jump. Neurological examination showed findings compatible with peripheral nervous system involvement. Histopathological findings revealed a high grade non-B, non-T cell renal lymphoma and peripheral neuropathy characterised by demyelination, axonal degeneration and muscle denervation. In the absence of congenital, metabolic and infectious diseases or exposure to toxins, a paraneoplastic peripheral neuropathy was hypothesised. In humans and dogs, paraneoplastic peripheral neuropathies have been documented with different neoplastic processes including lymphoproliferative disorders. To the authors' knowledge, this is the first report of suspected paraneoplastic polyneuropathy in a cat with malignant tumour.

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A 12-year-old, domestic shorthair neutered male cat, living in an apartment and fed with commercial cat food, was referred for progressive limb weakness lasting 2 weeks. The owner reported that the cat had presented weight loss for about 2 months although appetent with no gastrointestinal signs, polyuria or polydypsia. On admission, clinical parameters, such as temperature, heart rate, respiration, pulse, mucosal membranes, capillary refill time, blood pressure and palpable lymph nodes were normal. On abdominal palpation, bilateral renomegaly with irregular protrusions was detected. Generalised muscle wasting and atrophy, especially on distal portion of the limbs, were also noted. In sternal recumbency, the cat assumed a peculiar posture on forelimbs with bilateral flexion of the carpi and extrarotation of forearms. When stimulated, the cat was ambulatory but tetraparetic. The peculiar posture of the carpi was maintained even during deambulation. It was unable to go upstairs or jump. Neurological examination showed postural reactions mildly diminished on fore and hind limbs, marked withdrawal hyporeflexia of all limbs, normal bilateral patellar reflex and absent extensor carpi radialis reflex on both sides. Superficial and deep nociception was present. Evaluation of mental status and cranial nerves proved normal. These findings were compatible with peripheral nervous system (PNS) involvement. Blood samples were taken for routine laboratory evaluation. Haematology and serum biochemistry parameters were unremarkable. Urinalysis showed mild proteinuria (Table 1). Feline leukaemia virus (FeLV) and feline immunodeficiency virus (FIV) tests to detect, respectively, FeLV p27 antigen and FIV antibodies in serum, were both negative as was urine culture. IgM and IgG titres against *Toxoplasma gondii* were both negative. Total thyroxine (1.7 μg/dl, reference range 0.6–3.6 μg/dl) and free thyroxine (11 pg/dl, reference range 7.0–24.0 pg/dl) were within the reference range. Thoracic and spine radiographies did not identify any abnormalities. Abdominal ultrasonography detected the right kidney with normal echogenicity, preservation of corticomedullary definition but a roundish isoechoic mass (2.3 cm in diameter) deforming the cranial pole. The left kidney appeared enlarged with disordering of the normal structure and hypoechoic areas that cause considerable distortion of the renal contour. On the basis of this finding, a bilateral renal tumour was suspected. In the absence of metabolic and infectious

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Table 1. Serum biochemistry, complete blood count and urinalysis

	Results	Reference range
Serum biochemistry		
Glutamic-pyruvic transaminase (U/l)	36	30–100
Glutamic-oxalacetic transaminase (U/l)	52	12–56
Alkaline phosphatase (U/l)	32	25–93
Creatine kinase (U/l)	79	59–527
Creatinine (μmol/l)	133.5	70.7–159.1
Urea (mmol/l)	19.6	15.3–22.9
Total protein (g/l)	73	54–78
Albumin (g/l)	35	30–46
Globulin (g/l)	12.3	8–19
Phosphorous (mmol/l)	1.9	1.45–2.6
Total calcium (mmol/l)	2.4	1.6–2.6
Potassium (mmol/l)	4.3	4–4.5
Sodium (mmol/l)	153.4	147–156
Glucose (mmol/l)	5.3	4.05–7.4
Triglycerides (mg/dl)	85	10–114
Complete blood count		
Red blood cells ($\times 10^{12}$/l)	8.03	6.0–10.1
Haematocrit (volume fraction)	0.39	0.28–0.5
Haemoglobin (g/l)	140	81–142
White blood cells ($\times 10^{9}$/l)	9.37	6.3–19.6
Neutrophils ($\times 10^{9}$/l)	5.37	3–13.4
Lymphocytes ($\times 10^{9}$/l)	3.01	2–7.2
Monocytes ($\times 10^{9}$/l)	0.11	0–1
Eosinophils ($\times 10^{9}$/l)	0.87	0.3–1.7
Basinophils ($\times 10^{9}$/l)	0.01	0–0.1
Thrombocytes ($\times 10^{9}$/l)	197	156.4–626.4
Urinalysis		
Specific gravity	1.037	1.035–1.060
pH	6.5	6–7
Protein	2+	0 to trace
Glucose	Negative	Negative
RBC/HPF*	<1	(<5)
WBC/HPF†	<1	(<5)
Crystals	None	Occasional

*Red blood cells/high power field.
†White blood cells/high power field.

diseases or any exposure to toxins, a peripheral neuromyopathy was hypothesised. Fine-needle aspirates of the renal mass, acetylcholine receptor (AchRs) antibody titre evaluation, muscle and nerve biopsies were recommended but were not carried out at the owner's request. Symptomatic care consisted of administration of prednisone (1 mg/kg bid, OS: Deltacortene; Bruno Farmaceutici) to improve the neurological condition and an energy-dense diet (a/d, Hill's) to oppose the weight loss. One month later, the cat manifested no clinical signs of renal insufficiency but the neurological condition worsed. The cat was very weak, unable to rise and stand without assistance. At the owner's request, it was euthanased.

At necropsy, severe and diffuse muscular atrophy was identified. Abdominal post-mortem examination revealed the presence of voluminous masses bilaterally involving the renal cortices. The left kidney was totally destroyed by a voluminous, necrotic and haemorrhagic proliferation. The right kidney showed a circumscribed mass located on the cranial pole. Samples of the lung, heart, liver, spleen, pancreas, mesenteric lymph nodes, intestine, kidney, brain, spinal cord, muscle and nerves were fixed in 10% buffered formalin, routinely processed and stained with haematoxylin and eosin. Significant lesions in kidneys, muscle and nerves were found. Renal neoplastic tissue was characterised by round to ovoid cells infiltrating the interstitium and frequently forming round structures like lymphoid folliculi. Necrosis, haemorrhage and granulation tissue were present. Neoplastic cells relatively uniform in shape and size presented round to ovoid nuclei with dispersed or finely clumped chromatin and central nucleolus. Cytoplasms were inconstant sometimes abundant, sometimes moderate, but always visible. Numerous mitosis were detected. Apoptotic figures were frequently observed and numerous giant cells like phagocytes were observed especially in the left kidney tumour. Immunophenotypic studies were performed with CD3 and CD79a antibody stains to assess for T-cell and B-cell immunoreactivity, respectively. Cytokeratins immunopositivity was evaluated to exclude carcinomas; CD18 and CD20 immunostaining to exclude histiocytic disease. The neoplastic cells were negative for all markers. The histological and immunohistochemical features were consistent with a diagnosis of high grade non-B, non-T cell lymphoma according to the World Health Organization International Histological Classification of Tumors of Domestic Animals.[1] The morphological features support the presence of a neoplastic process possibly of natural killer (NK) cell origin. However, NK cell origin cannot be proven because specific required antibodies are not available for feline tissues.

Nerve sections (common peroneal, ulnar and radial nerves) showed most of the myelin sheaths replaced by numerous large vacuoles containing granular material. Varying degrees of myelin loss were observed. There was an increased number of Schwann cell nuclei and numerous macrophages within the myelin sheaths. Numerous digestion chambers were detected containing central axon fragments and ovoids of degenerated myelin (Fig 1). Muscle tissue (biceps femoris and triceps brachii muscles) revealed moderate atrophic fibres which had an anguloid shape. These changes were consistent with peripheral neuropathy characterised by axonal degeneration and muscle denervation. Neither

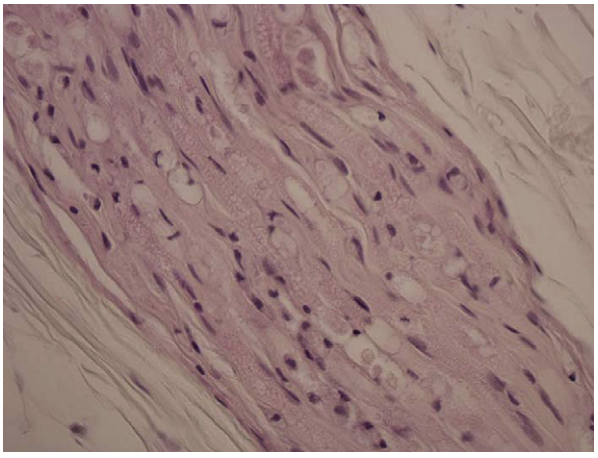

Fig 1. Section of radial nerve: diffuse and severe degeneration of the myelin sheaths replaced by numerous large vacuoles containing granular material. Evident digestion chambers containing central axon fragments and ovoids of degenerated myelin. Haematoxylin and eosin, 400×.

aetiological agents nor metastatic infiltration was observed in tissues.

Peripheral neuropathy occurs infrequently in cats. A number of aetiologies have been described including inherited disorders; endocrine diseases such as diabetes mellitus and hyperthyroidism; infectious diseases such as FeLV and FIV; nutritional disorders such as phenylalanine and tyrosine deficiency; intoxication by organophosphate, carbamate, heavy metals, salinomycin and acrylamide; drugs such as aminoglycosides and vincristine and acute or chronic idiopathic polineuropathy.[2,3] Moreover, a neoplastic process may involve the PNS by development of primary neural tumours or by metastatic infiltration. Finally, the PNS can be the target of paraneoplastic effects which are not directly attributable to malignant invasion.[4,5] Paraneoplastic neuropathy can affect any part of the central and PNS, and the neuromuscular junction.[6,7] Neurological disorders can develop before the cancer becomes clinically overt and can progress rapidly leaving patients severely debilitated within weeks to months. In most cases, severity of paraneoplastic neuropathy is due to early and non-reversible destruction of neural structures.[7] Paraneoplastic peripheral neuropathies (PPN) may be purely sensory, others may be motor or autonomic, and many are sensory-motor. The peripheral sensory or motor neuron cell body, the axons, the myelin sheath, or the presynaptic axonal end may be the target of the lesioning process. In humans, a great variety of tumours are associated with PPN.[7–9] In dogs, PPN have been documented predominantly in association with insulinoma besides sarcoma, carcinoma, lymphoma, melanoma, and mast cell tumour.[4,10–16] In cats, thymoma was previously associated with neuromuscular junction disorders such as myasthenia gravis.[17,18] To the author's knowledge, this is the first report of suspected paraneoplastic polyneuropathy in a cat with malignant tumour. In this case, congenital disorders, metabolic and infectious diseases or exposure to toxins and drugs known to cause polyneuropathy were excluded. The authors suspected that peripheral nerve lesions represent a paraneoplastic effect of lymphoma on the PNS. In retrospect, an AchRs antibody titre should have been evaluated to definitively exclude myasthenia gravis. However, this disease would be unable to cause the histopathological changes seen in this cat. The nerve lesions found in this case, characterised by demyelination and axonal degeneration, are usually observed in humans and dogs suspected of having peripheral neuropathy associated with malignant tumours including lymphoproliferative disorders.[4,6,8,14,16] Lymphoma is a common haematopoietic neoplasm of the cat.[19] The kidneys are frequently involved especially in older cats. Although renal lymphoma may appear unilateral, it is nearly always bilateral.[20] It appears to be mainly B-cell in origin and often presents with acute-onset renal insufficiency.[21] This cat developed an high grade non-B, non-T cell lymphoma but there was no renal insufficiency. Weight loss was probably caused by cancer cachexia that is a common effect of malignant tumour associated with abnormalities in carbohydrate, lipid and protein metabolism.[22] Above all, increased protein catabolism and decreased protein synthesis might have contributed to muscle atrophy along with denervation. Several hypotheses have been proposed regarding the pathogenesis of PPN. Actually, the only demonstrated links between a tumour and paraneoplastic neuropathy involve immunological mechanisms. The discovery of onconeural antibodies directed against antigens expressed by both the tumour and the nervous system has suggested that PPN could be an immune-mediated disorder.[5,7] Other suggested pathogeneses include the elaboration of a neurotoxic substance by the tumour, nutritional deficiencies, vascular effects on the nervous system, viral infection and alteration of homeostatic endocrine functions.[6] To date, the best way to stabilise paraneoplastic neuropathy is to treat the cancer. Immunotherapy is rarely effective, but some patients have improved with the use of immunoglobulins, steroids or plasmapheresis.[6,7] In our case, chemotherapy to treat lymphoma was not carried out and the administration of prednisone did not improve the neurological condition. However, in this case it is impossible to exclude that the cat developed an idiopathic peripheral neuropathy and that the association with the lymphoma was purely coincidental. In conclusion, nevertheless it is difficult to establish a causal relationship between the tumour and neurological clinical signs, the possibility of underlying cancer should be considered in cats presented for neuromuscular disorders, especially those in which another aetiology cannot be found.

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