Renal adenocarcinoma associated with hypertrophic osteopathy in a cat

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Abstract
Case summary A 10-year-old neutered male domestic shorthair cat was diagnosed with renal adenocarcinoma associated with hypertrophic osteopathy. The cat was referred for chronic ambulation difficulties. The physical examination showed a painful thickening of all four limbs, a right cranial abdominal mass and a conjunctival hyperaemia. Radiographic findings were consistent with extensive periosteal new bone formation involving not only the diaphyses of the fore- and hindlimbs, but also of the pelvis, tarsus and carpus. Abdominal ultrasonography and CT revealed a mass within the right kidney and a primary neoplasm was suspected. A ureteronephrectomy of the right kidney was performed and histopathology confirmed the diagnosis of renal adenocarcinoma. Although clinical improvement of the lameness occurred after surgery, no radiographic changes of hypertrophic osteopathy lesions were observed at the 9-month follow-up.

Relevance and novel information Feline cases of hypertrophic osteopathy are rarely reported in the literature and only a few of them were associated with abdominal neoplastic diseases. To our knowledge, this is the first case of renal adenocarcinoma associated with hypertrophic osteopathy in a cat.

Keywords: Hypertrophic osteopathy; renal adenocarcinoma; ureteronephrectomy

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Introduction
Hypertrophic osteopathy (HO) is characterised by periosteal bone proliferation involving the diaphyses of long bones and digits. The periosteal proliferation is mostly symmetrical but can be variable in appearance (nodular, speculated or palisade patterns). Clinically, HO is usually associated with painful and swollen limbs causing difficulty in ambulation or lameness. In some cases, inappetence or anorexia associated with weight loss are also described. HO is a rare syndrome already described in many species, including horses, cattle, wild animals, dogs, cats and humans. In dogs, it is usually associated with pulmonary or intrathoracic diseases, especially neoplasms, but granulomatous diseases (Spirocerca lupi), abscesses and endocarditis (bacterial, Dicrofilaria immitis) are also described as inciting conditions. Some cases of canine HO have been associated with intra-abdominal neoplasms without any intrathoracic involvement. In cats, only a few cases of HO have been previously published associated with intrathoracic, adrenal or renal...
neoplastic diseases. This syndrome also has been described in association with megaesophagus, nutritional causes, congenital heart defect and with injection-site sarcoma in cats, and also idiopathic causes. Both prognosis and therapeutic management of HO depend on the underlying cause.7

Case description
A 10-year-old neutered male domestic shorthair cat (body weight 4.7 kg) was referred with several months’ history of stiff and impaired gait and weight loss, which worsened in the month prior to admission. Nutraceuticals (Arthrosenior Chat; Laboratoires Clément Thékan) were previously prescribed by the referring veterinarian for suspected osteoarthritis of the hips. One capsule of the glucosamine–chondroitin supplement (glucosamine hydrochloride 50 mg, chondroitin sulfate 46 mg, ascorbic acid 15.6 mg) was administered q24h PO for 15 days without clinical improvement. The main abnormalities detected on physical and orthopaedic examination included hindlimb stiffness, reluctance to move and thickening of all four limbs (Figure 1). The range of motion of the stifles, hips, tarsi, carpi and elbows was also decreased, and manipulation of the long bones was painful. The cat also showed moderate bilateral conjunctival hyperaemia. Abdominal palpation was not painful, but a firm mass was noted, in the right sublumbar fossa. The size of both kidneys was increased but asymmetrically, with the right kidney larger than the left one. Thoracic auscultation revealed a left-sided 3/6 apical systolic heart murmur.

Complete blood count abnormalities included mild leukocytosis (17.7 × 10⁹ cells/l; reference interval [RI] 6.0–11.0 cells/l), neutrophilia (15.1 × 10⁹ cells/l; RI 3.0–11.0 cells/l) and monocytosis (0.67 × 10⁹ cells/l; RI 0.04–0.5 cells/l). Biochemistry parameters and the coagulation profile were within the RIs. Urine was collected via cystocentesis and urinalysis showed a specific gravity within the normal range (1.038), mild proteinuria and haematuria on dipstick, and no abnormalities on microscopic examination of the urinary sediment. Urine culture was negative 48 h after culture.

Radiographic examination of thoracic and pelvic limbs, abdomen and thorax was performed without sedation. Positioning of the cat was obtained with manual restraint, in accordance with the radiation safety regulations. Orthogonal radiographic views revealed extensive periostal new bone formation involving the diaphysis of the radius, ulna, tibia and fibula, and metacarpal and metatarsal bones bilaterally but associated with soft tissue thickening of the extremities. There were also changes on the pelvis (ischium and ilium). The radiographic appearance of the periosteal proliferation was variable (brush-like on extremities, and thin and regular on long bones and pelvis) (Figure 2). Abdominal radiographs revealed an increased right kidney size (length 7.5–8 cm). Punctiform mineralisations were also observed in the projection area of the right kidney and were consistent with renal parenchymal calcification. Another calcification was identified dorsal to the bladder neck and ventral to the colon, consistent with a distal left ureterolith. No relevant radiographic abnormality was noted on thoracic radiographs; in particular, neither primary nor metastatic pulmonary tumours nor cardiomegaly were detected.

Abdominal ultrasound findings included moderately increased size (4.8 cm) of the left kidney with an irregular and hyperechoic edge, thickened cortical layer and decreased delimitation of the corticomedullary junction. Moderate pyelectasia was also noted without ureteral dilatation. A ureterolith was also observed in the distal part of the left ureter, as well as intraluminal hyperechoic particles in the bladder. The normal anatomical structure of the right kidney was lost as a result of an intraparenchymal, irregular heterogeneous and hypoechoic mass (6 × 4 cm) with irregular edges, almost totally effacing the normal architecture, compressing the renal pelvis and sparing only the caudal pole. An echocardiogram was performed to explore the left-sided apical systolic heart murmur and showed degenerative mitral valve disease without atrial enlargement.

Figure 1 Thickening of the left hindlimb
A full body CT examination was performed under general anaesthesia to increase the sensitivity of detection of primary and metastatic tumours and to better define the renal lesion. The cat was premedicated with midazolam (Hypnovel; Roche) 0.2 mg/kg IV and butorphanol (Torbugesic; Zoetis) 0.2 mg/kg IV. General anaesthesia was induced with propofol (Rapinovet; Intervet) 5 mg/kg IV to effect and maintained with isoflurane (Vetflurane; Virbac) administered with 100% oxygen. The CT examination confirmed subtotal invasion of the renal parenchyma by a tumour that displayed closed contact with the vena cava without invading it or the right adrenal gland (Figure 3). The CT scan also confirmed the presence of a ureterolith of 2.5 mm in diameter located cranially to the left ureterovesical junction without signs of obstruction. There was no evidence of pulmonary metastasis, but a mild enlargement of the suprasternal lymph node was noted.

Ultrasound-guided biopsies of the right kidney mass using a Tru-Cut (18G needle) was performed on the following day under generalised anaesthesia with a standardised protocol combining diazepam (Valium; Laboratoire Roche) 0.2 mg/kg IV, propofol (Rapinovet; Intervet) 5 mg/kg IV and isoflurane (Vetflurane; Virbac) administered in 100% oxygen. Fluid therapy (NaCl 0.9% [B Braun; Virbac]) and analgesia with morphine (Morphine Chlorhydrate; Renaudin) 0.3 mg/kg IV q4h were provided. The patient was hospitalised during the day to be monitored for postbiopsy complications and an abdominal ultrasound was performed before discharge to rule out abdominal haemorrhage. Histological diagnosis was renal adenocarcinoma.

Surgical excision of the right renal tumour was then planned. Premedication was performed with methadone (Mephenon; Sterop) 0.2 mg/kg IV and diazepam (Valium; Laboratoire Roche) 0.2 mg/kg IV. General anaesthesia was induced with propofol (Rapinovet; Virbac) 5 mg/kg IV to effect and maintained with sevoflurane (Sevoflurane Baxter; Baxter) administered in 100% oxygen. Intraoperative constant rate infusion (CRI) of fentanyl (Fentanul Mylan; Laboratoires Mylan) 2 μg/kg/h and ketamine (Imalgene; Boehringer Ingelheim) 0.15 mg/kg/h was administered for analgesia. The abdomen was approached through a midline celiotomy. Exploration of
the abdominal cavity confirmed a voluminous mass deforming the right kidney, displaying a close contact and indistinguishable anatomical boundaries with the right adrenal gland and deviating the caudal vena cava towards the left. An en-bloc right ureteronephrectomy and right adrenalectomy was performed. The ligatures were placed around renal and phrenic-abdominal veins and arteries before setting up haemostatic clips on collateral vessels. A simple circumferential ligature (PDS 2.0) transfixing the bladder wall was placed in the most distal part of the right ureter leaving the smallest ureteral stump possible (Figure 4). The left ureter was not dilated and a gentle palpation was applied on the ureterolith in order to advance this into the bladder. All excised tissue was submitted to histological examination. This revealed a multilobulated neoplasm circumscribed by connective tissue forming a capsule compatible with a renal adenocarcinoma associated with mild necrosis and rare lymphoplasmocytic infiltrates. No vascular embolism of neoplastic cells or ipsilateral adrenal gland infiltration were observed.

The cat recovered uneventfully from the anaesthesia and surgery, and intravenous fluid and analgesia were provided postoperatively. CRI of fentanyl (Fentanyl Mylan; Laboratoires Mylan) 2 μg/kg/h and ketamine (Imalgene; Boehringer Ingelheim) 0.15 mg/kg/h was continued 3h after surgery and then replaced with morphine (Morphine Chlorhydrate Aguettant; Laboratoire Aguettant) 0.3 mg/kg q4h SC tapered to 0.1 mg/kg q4h SC on the following day. Renal parameters (urea, creatinine), packed cell volume, total proteins and serum albumin concentrations were monitored during the hospitalisation period. Transient anaemia...
(erythrocytes $3.39 \times 10^{12}$ cells/l [RI: 6.54–12.20 $\times 10^{12}$ cells/l]; haematocrit 15.4% [RI: 30.3–52.3%]; haemoglobin 5.7g/l [RI: 9.8–16.2g/l]) and hypoproteinaemia (48g/l; RI 57–89 g/l) were detected. They were thought to most likely be due to haemodilution or blood loss during the surgery as they showed complete resolution after a few days. Renal parameters remained within the normal RIs. Abdominal ultrasound was performed 3 days after surgery and no relevant abnormality was detected.

The cat was discharged 5 days postoperatively and was monitored at 2 weeks and 1, 2, 4, 5 and 9 months after surgery to follow renal function and the evolution of bone lesions. Clinical improvement was evident 2 weeks after surgery with an increase in physical activity and appetite. Conjunctival hyperaemia was also noted to have resolved. The thickening of all four limbs was decreased on palpation, and the lameness resolved at the 2- and 4-month follow-ups, respectively. Urinalysis performed at each postoperative assessment remained within the normal range and urine culture was still negative 1 month after surgery. Abdominal ultrasound was performed 1 month postoperatively and findings were similar to the immediate postoperative examination. Serum biochemistry, including urea, creatinine, albumin and total protein concentration, was performed at the 1-, 2- and 5-month follow-ups and was within the RIs. Persistent radiographic changes consistent with hypertrophic osteopathy were identified on radiographic survey of all four limbs performed at each follow-up. The cat was lost to follow-up after this time.

**Discussion**

Only 20 feline cases of HO are reported in the literature.1,2,4–7,21–30 Among them, nine were associated with neoplastic diseases, including intrathoracic neoplasia (n = 5),21,23–26 injection site sarcoma (n = 1),27 adenocortical carcinoma without pulmonary metastasis (n = 1)1 and renal adenoma (n = 2).7,22 Only two previously reported feline cases were associated with renal tumours, and both were benign (papillary and tubular adenomas) without thoracic involvement.7,22

The case reported here is therefore the first described feline case of HO associated with a malignant renal neoplasia. Primary renal tumours are rare in cats according to a retrospective study carried out in the USA between 1992 and 1998.32 During this period, only 19 cases have been diagnosed and the most frequent tumours were carcinomas (11 papillary and two tubulo-papillary types). None of these cases was associated with HO.32

HO is a syndrome clinically characterised by pain and swelling of the limbs, and difficulty in ambulation or lameness; anorexia or decreased appetite associated with weight loss can also be observed.1–5 The case described here showed all of the above mentioned clinical and orthopaedic abnormalities.

The pathogenesis of periosteal proliferation is still not completely understood and seems to be multifactorial as suggested by several publications on human and canine HO.19,33 Hyperperfusion of appendicular tissue secondary to arterial vasodilatation and overgrowth of vascular connective tissue in the extremities is suspected to be the main mechanism leading to bone spicule formation.34–36 In humans, several humoral factors seemed to be incriminated in the pathogenesis, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and inflammatory cytokines.36–38 It has been hypothesised that increased blood concentrations of VEGF and/or PDGF could induce fibrovascular proliferation, oedema and possible new periosteal bone formation.39 Increased blood concentration of these two factors in human patients with HO secondary to lung tumours was detected in comparison with patients having pulmonary tumour without HO.37 The production of humoral factors in human patients with paraneoplastic HO without intrathoracic lesions is also considered a likely hypothesis.40 However, the neurogenic hypothesis suggests the presence of nervous reflex originating from the thoracic part of the vagus nerve causing stimulation of the blood circulation of the limbs.33,35,41 HO associated with extrapulmonary lesions is thought to follow the distribution of nasopharyngeal and vagus nerves that carry fibres innervating vascular tissues, which further strengthens the neuromuscular reflex theory.42 Finally, increased growth hormone, tissue hypoxia and circulating toxic products for synovial membranes and periosteum released from primary lesion are also possible mechanisms incriminated in the genesis of HO.35,36,43

Another noticeable clinical sign observed in this case was the bilateral conjunctival hyperaemia. Ocular modifications have been described in two previous feline case reports with HO secondary to neoplasia.1,9 One case presented similar conjunctival hyperaemia with mucopurulent ocular discharge.6 The other feline case had vascular modifications in the posterior segment.1 In both cases, as well in the present case, the ocular modifications resolved spontaneously after surgical removal of the tumour. The pathogenesis of ocular modification associated with HO remains unclear and speculative.1,6 It has been suggested that ocular signs could be secondary to systemic vasoactive modifications incriminated in the pathogenesis of HO or could represent a paraneoplastic syndrome.6 Two studies on canine HO including 30 dogs each have reported conjunctival hyperaemia and ocular discharge in 33% and 66%, respectively.44,45 However, conjunctival hyperaemia remains a non-specific ocular sign and could be related to other pathological conditions. In the cat described here, specific tests to rule out infectious or non-infectious conditions should have been performed. Thus, association remains speculative.
When a unilateral ureteronephrectomy is performed, it is crucial to be sure that the remaining kidney will be capable of sustaining the patient’s life. In our specific case a left ureterolith was present, but no further surgical procedure was elected for this. Because of the subtotal neoplastic invasion of the right kidney, it was assumed that the left kidney was functional, and preoperative normal serum creatinine concentration and urinalysis were not supportive of a major left kidney disease. Further, the left ureter patency was indirectly confirmed during the CT examination. Usual filtration and excretion of the intravenous contrast medium by the left kidney and through the left ureter lead the authors to speculate that the left ureterolith was not obstructive.

Both prognosis and therapeutic management of HO depend on the underlying cause. In several studies, curative treatment of underlying causes led to complete regression of this syndrome. Indeed, surgical removal of tumours, modification of food or management of the megaesophagus led to complete regression of HO in 15 weeks to 24 months. The cat in the present report displayed orthopaedic clinical improvement after surgical excision of the renal carcinoma while radiographic lesions of HO were still present 9 months after the surgery. The persistence of radiographic lesions could be due to a short-term follow-up or, perhaps, to other additional underlying causes or unidentified metastasis. These hypotheses are considered less likely by the authors owing to the overall clinical improvement of the cat. Several case reports have described a complete regression of paraneoplastic HO between 12 and 24 months after surgical removal of the underlying neoplasia in dogs. In two of these cases, HO was secondary to a renal carcinoma. However, of four recent feline cases of HO associated with malignant neoplastic disease, one was euthanised, one died 2 months after the surgical removal of the tumour secondary to disseminated metastasis, and two had significant radiographic improvement of the HO 4 and 6 months after the surgery. It is therefore difficult to draw a definite conclusion about the radiographic evolution in the cat and the limited number of cases makes the comparison even more challenging.

Conclusions
To our knowledge, this is the first case of renal adenocarcinoma associated with HO in a cat. Despite complete surgical excision and absence of macroscopic metastasis, persistence of the radiographic lesions was noted until the 9-month follow-up. Further radiographic follow-up would have been interesting in this case to monitor the evolution of the periosteal bone proliferation. This case is also the third description of feline HO possibly associated with ocular abnormalities and the second case of conjunctival hyperaemia. A possible relationship between the two entities remains to be investigated.

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Ethical approval
This work involved the use of non-experimental animals only (including owned or unowned animals and data from prospective or retrospective studies). Established internationally recognised high standards (‘best practice’) of individual veterinary clinical patient care were followed. Ethical approval from a committee was therefore not necessarily required.

Informed consent
Informed consent (either verbal or written) was obtained from the owner or legal custodian of animal(s) described in this work (either experimental or non-experimental animals) for the procedure(s) undertaken (either prospective or retrospective studies). No animals or humans are identifiable within this publication, and therefore additional informed consent for publication was not required.

References
1 Becker TJ, Perry RL and Watson GL. Regression of hypertrophic osteopathy in a cat after surgical excision of an adenocortical carcinoma. J Am Anim Hosp Assoc 1999; 35: 499–505.
2 de Melo Ocarino N, Fukushima FB, de Matos Gomes A, et al. Idiopathic hypertrophic osteopathy in a cat. J Feline Med Surg 2007; 8: 345–348.
3 Chiang YC, Liu CH, Ho SY, et al. Hypertrophic osteopathy associated with disseminated metastases of renal cell carcinoma in the dog: a case report. J Vet Med Sci 2007; 69: 209–212.
4 Huang CH, Jeng CR, Lin CT, et al. Feline hypertrophic osteopathy: a collection of seven cases in Taiwan. J Am Anim Hosp Assoc 2010; 46: 346–352.
5 Mills J. Hypertrophic osteopathy and megaesophagus in a cat. Vet Comp Orthop Traumatol 2010; 23: 218–222.
6 Grierson JM, Burton CA and Brearley MJ. Hypertrophic osteopathy secondary to pulmonary sarcoma in a cat. Vet Comp Oncol 2003; 1: 227–231.
7 Johnson RL and Lenz SD. Hypertrophic osteopathy associated with a renal adenoma in a cat. J Vet Diag Invest 2011; 23: 171–175.
8 Mair TS, Dyson SJ, Fraser JA, et al. Hypertrophic osteopathy (Marie’s disease) in Equidae: a review of twenty-four cases. Equine Vet J 1996; 28: 256–262.
Hypertrophic pulmonary osteoarthropathy.

28 Foster SF. Idiopathic hypertrophic osteopathy in a cat. J Feline Med Surg 2007; 9: 172–173.

29 de Castro Guizelini C, Mattei RR, Pupin RC, et al. Osteopatia hiperтрофica idiopatica em um gato. Acta Sc Vet 2019; 47 Suppl 1: 373.

30 de Soussa FAB, Bianchi MV, Taunde PA, et al. Hypertrophic osteopathy in a cat with cardiac interventricular septal defect. J Vet Sci 2019; 20: e52. DOI: 10.4142/jvs.2019.20.e52.

31 Armbrust LJ, Biller DS, Bamford A, et al. Comparison of three-view thoracic radiography and computed tomography for detection of pulmonary nodules in dogs with neoplasia. J Am Vet Med Assoc 2012; 240: 1088–1094.

32 Henry CJ, Turnquist SE, Smith A, et al. Primary renal tumours in cats: 19 cases (1992–1998). J Feline Med Surg 1999; 1: 165–170.

33 Watson AD and Porges WL. Regression of hypertrophic osteopathy in a dog following unilateral intrathoracic vagotomy. Vet Rec 1973; 93: 240–243.

34 Ginsburg. Observation on the peripheral circulation of hypertrophic pulmonary osteopathy. Q J Med 1958; 107: 335–352.

35 Lenehan TM and Fetter AW. Hypertrophic osteopathy. In: Newton CD and Nunemaker DM (eds). Textbook of small animal orthopedics. Philadelphia, PA: Lippincott William & Wilkins, 1985, pp 603–609.

36 Dickinson CJ and Martin JF. Megakaryocytes and platelet clumps as the cause of finger clubbing. Lancet 1987; 2: 1434–1435.

37 Silveira LH, Martinez-Lanvin M, Pineda C, et al. Vascular endothelial growth factor and hypertrophic osteopathy. Clin Exp Rheumatol 2000, 18: 57–62.

38 Shih WJ. Pulmonary hypertrophic osteoarthropathy and its resolution. Semin Nuc Med 2004, 34: 159–163.

39 Atkinson S and Fox SB. Vascular endothelial growth factor (VEGF)-A and platelet-derived growth factor (PDGF) play a central role in the pathogenesis of digital clubbing. J Pathol 2004, 203: 721–728.

40 Manuel ML. Exploring the cause of the most ancient clinical sign of medicine: finger clubbing. Semin Arthritis Rheum 2007, 36: 380–385.

41 Flavell G. Reversal of pulmonary hypertrophic osteopathy by vagotomy. Lancet 1956, 270: 260–262.

42 Četinkaya CA, Yaridmicı B and Yaridmicı C. Hypertrophic osteopathy in a dog associated with intra-thoracic lesions: a case report and a review. Vet Med-Czech 2011, 56: 595–601.

43 Greenberg PB, Beck C, Martin TJ, et al. Synthesis and release of human growth hormone from lung carcinoma in cell culture. Lancet 1972, 12: 350–352.

44 Withers SS, Johnson EG, Culp WTN, et al. Paraneoplastic hypertrophic osteopathy in 30 dogs. Vet Comp Oncol 2015, 13: 157–165.

45 Salvasurenko M, Peeri D, Bibring U, et al. Hypertrophic osteopathy: a retrospective case control study of 30 dogs. Isr J Vet Med 2015, 68: 209–217.

46 Toboa KM and Tillson DM. Kidneys. In: Jonhston SA and Tobias KM (eds). Veterinary surgery small animals. 2nd ed. St Louis, MO: Elsevier, 2018, pp 2184–2201.