

Primary hyperparathyroidism caused by bilateral parathyroid cystic carcinoma in a cat

Authors: Virtanen, Juulia K, Mölsä, Sari H, Hagner, Karoliina A, Salonen, Hanna M, and Kilpinen, Susanne

Source: Journal of Feline Medicine and Surgery Open Reports, 6(2)

Published By: SAGE Publishing

URL: <https://doi.org/10.1177/2055116920976544>

BioOne Complete (complete.BioOne.org) is a full-text database of 200 subscribed and open-access titles in the biological, ecological, and environmental sciences published by nonprofit societies, associations, museums, institutions, and presses.

Your use of this PDF, the BioOne Complete website, and all posted and associated content indicates your acceptance of BioOne's Terms of Use, available at www.bioone.org/terms-of-use.

Usage of BioOne Complete content is strictly limited to personal, educational, and non - commercial use. Commercial inquiries or rights and permissions requests should be directed to the individual publisher as copyright holder.

BioOne sees sustainable scholarly publishing as an inherently collaborative enterprise connecting authors, nonprofit publishers, academic institutions, research libraries, and research funders in the common goal of maximizing access to critical research.



Primary hyperparathyroidism caused by bilateral parathyroid cystic carcinoma in a cat

Juulia K Virtanen¹, Sari H Mölsä¹, Karoliina A Hagner², Hanna M Salonen³ and Susanne Kilpinen¹ 

Journal of Feline Medicine and Surgery Open Reports
1–6

© The Author(s) 2020

Article reuse guidelines:

sagepub.com/journals-permissions

DOI: 10.1177/2055116920976544

journals.sagepub.com/home/jfmsopenreports

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



Abstract

Case summary A 16-year-old neutered female Korat cat presented with chronic vomiting, mild azotaemia and mild hypercalcaemia. Physical examination revealed bilateral palpable masses on each side of the trachea. Laboratory results were consistent with primary hyperparathyroidism, diagnostic imaging findings with cystic thyroid or parathyroid masses, and fine-needle aspiration cytology with thyroid hyperplasia or adenoma. In order to confirm whether one or two of the masses were the cause of the hyperparathyroidism, cystic fluid was aspirated from both for parathyroid hormone concentration measurement. The concentration was shown to exceed that of the serum manyfold in both samples, confirming both masses to be functional and of parathyroid origin. A total parathyroidectomy and thyroidectomy were performed on the right side, and a subtotal thyroidectomy and a subtotal to total parathyroidectomy on the left, without any major postoperative complications. Histopathology was consistent with bilateral parathyroid carcinoma.

Relevance and novel information To our knowledge, this report is the first to describe a rare case of bilateral parathyroid cystic carcinoma in a cat. It highlights the usefulness of determining parathyroid hormone concentration in the cystic fluid of a suspected neoplastic parathyroid mass preoperatively. It also demonstrates that it may be possible to remove most of the cervical parathyroid and thyroid tissue of a cat without causing any clinically relevant hypocalcaemia or iatrogenic hypothyroidism. However, serum concentrations of ionised calcium, thyroxine and creatinine should be closely monitored in the postoperative period in order to detect and control possible complications.

Keywords: Hypercalcaemia; parathyroid neoplasm; parathyroid hormone; cervical mass

Accepted: 27 October 2020

Case description

A 16-year-old neutered female Korat cat presented with vomiting, mild hypercalcaemia and mild azotaemia. Physical examination revealed two easily movable masses on the ventral cervical neck, with one on each side of the trachea in the region of the thyroid glands (Figure 1). The right mass measured approximately 2 × 1 cm and the left one 1 × 1 cm.

Complete blood count results were within the reference intervals (RIs). Serum biochemical analysis revealed mild hypercalcaemia (total calcium 3.17 mmol/l [RI 2.2–3.0 mmol/l] and ionised calcium [iCa] 1.57 mmol/l [RI 1.15–1.40 mmol/l]), moderate hypophosphataemia (0.69 mmol/l; RI 1.3–2.1 mmol/l), mild azotaemia (creatinine 183 µmol/l; RI <170 µmol/l) and mild

hyperglycaemia (7.9 mmol/l; RI 3.5–5.7 mmol/l). Serum parathyroid hormone (PTH) concentration was markedly increased (42.0 pg/ml; RI 7–26 pg/ml). PTH-related

¹Department of Equine and Small Animal Diseases, Faculty of Veterinary Medicine, University of Helsinki, Helsinki, Finland

²Department of Veterinary Biosciences, Faculty of Veterinary Medicine, University of Helsinki, Helsinki, Finland

³Department of Diagnostic Imaging, Faculty of Veterinary Medicine, University of Helsinki, Helsinki, Finland

Corresponding author:

Juulia K Virtanen DVM, Department of Equine and Small Animal Diseases, Faculty of Veterinary Medicine, University of Helsinki, PO Box 57, Helsinki, 00014, Finland
Email: juulia.virtanen@finnet.fi



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons

Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).



Figure 1 Photograph of the cat showing bilateral masses in the ventral cervical region

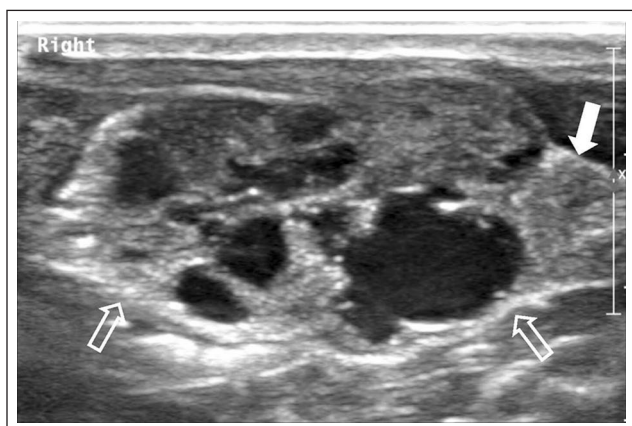


Figure 2 Ultrasonographic image of the triangular-shaped caudal pole of the right thyroid gland (solid arrow) and the large cystic soft tissue mass replacing the rest of the thyroid gland (open arrows) in a sagittal view

peptide (PTHrP) (<0.50 pmol/l; <0.8 pmol/l) and serum total thyroxine (T₄; 20 nmol/l [RI 10–60 nmol/l]) concentrations were within the RI. Urinalysis revealed a mildly decreased urine specific gravity (USG) of 1.033 (RI >1.035).

Abdominal ultrasonography revealed slightly decreased size and mildly increased cortical echogenicity of both kidneys. Cervical ultrasonography revealed a well-defined, mildly heterogeneous soft tissue mass, measuring 18 mm \times 9 mm, within the right thyroid gland, which measured 23 mm \times 10 mm. The mass contained multiple cysts with anechoic content, measuring up to 4 mm \times 6 mm (Figure 2). Normal thyroid tissue was identified at the caudal pole of the mass. The left thyroid gland, measuring 18 mm \times 7 mm, contained a single large cyst with anechoic content, measuring

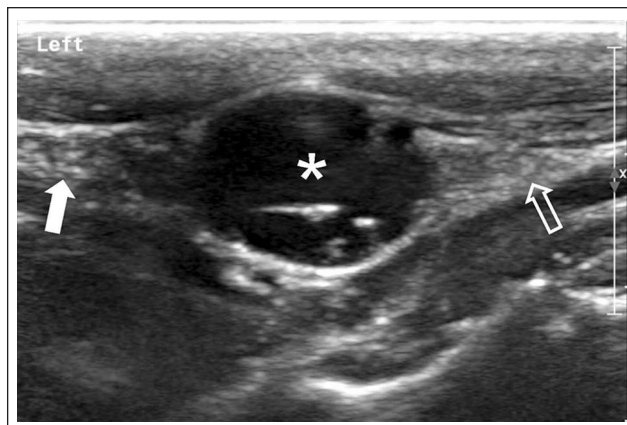


Figure 3 Ultrasonographic image of the cranial (solid arrow) and the caudal (open arrow) poles of the fusiform-shaped left thyroid gland and the parathyroid cyst (*) in a sagittal view

9 mm \times 6 mm. Normal thyroid tissue was identified at the cranial and caudal poles of the cyst (Figure 3).

Fine-needle aspiration (FNA) cytology of the right-sided mass revealed clusters of follicular epithelial cells with round, centrally placed nuclei and pale basophilic cytoplasm. The cells formed acinar-like structures surrounding eosinophilic colloid. Very mild anisokaryosis and anisocytosis were observed. These findings were consistent with neuroendocrine – most likely thyroid – hyperplasia or adenoma.

Cystic fluid was aspirated bilaterally under ultrasonographic guidance for the analysis of PTH concentration and was found to be clear and watery. A sample volume of 0.1–0.2 ml was yielded from both sides and diluted to the required minimum sample volume of 0.4 ml with sterile saline. Results showed the PTH concentration in the cystic fluid to exceed that in the serum (42.0 pg/ml; RI 7–26 pg/ml) manyfold (right cervical mass 12,081 pg/ml, left cervical mass 5199 pg/ml), confirming both masses to be functional and of parathyroid origin. CT of the cervical region and the thorax revealed no signs of metastatic disease or invasion of vital anatomical structures by the masses. While waiting for the test results, the patient was treated symptomatically with a renal diet, maropitant (1.7 mg/kg PO q24h) to reduce vomiting and half a teaspoon of psyllium mixed with wet food (q12h) in an attempt to reduce the hypercalcaemia. After the final diagnosis had been reached, surgery was pursued.

The patient was premedicated with levomethadone (0.2 mg/kg IV) and midazolam (0.2 mg/kg IV). Anaesthesia was induced with propofol (4 mg/kg IV). Following endotracheal intubation, anaesthesia was maintained with sevoflurane and a constant rate infusion of fentanyl (3–10 μ g/kg/h). At surgery, performed using a ventral midline approach to the thyroid area, no

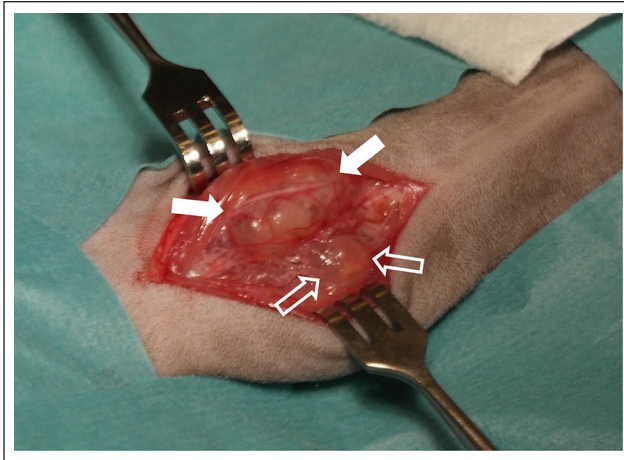


Figure 4 Intraoperative photograph showing the larger right-sided mass with multiple cysts (solid arrows) and the smaller left-sided mass containing only one visible cyst (open arrows)

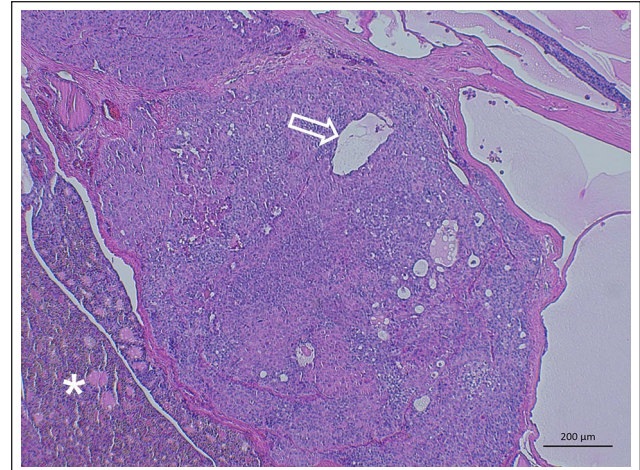


Figure 5 Histopathological image of the left-sided cystic parathyroid carcinoma (haematoxylin and eosin staining, $\times 50$ magnification) showing cyst formation (open arrow) and an area of normal thyroid tissue (*)

normal thyroid or parathyroid tissue was identified on the right side. Instead, a cystic mass was discovered and resected (Figure 4). The tissue at the site of the left thyroid gland was partially cystic and no normal parathyroid tissue was identified. The cystic tissue was resected and normal-looking thyroid tissue measuring 3–5 mm at the cranial and 2 mm at the caudal poles of the resection site was identified and preserved. Postoperative treatment during the 28 h hospitalisation period consisted of intravenous fluid therapy with Ringer's acetate solution, pain management with levomethadone (0.1–0.2 mg/kg IV q4h), a fentanyl patch (12 μ g/h) and maropitant (1 mg/kg IV q24h).

The cat recovered well. iCa concentration was re-evaluated every 4 h for the first 28 h, then once daily for 6 days and then once a week for the first month postoperatively. It reached its lowest point 19 days after the surgery (0.90 mmol/l; RI 1.15–1.40 mmol/l) and returned to the RI (1.17 mmol/l; RI 1.15–1.40 mmol/l) 25 days after surgery. No clinical signs of hypocalcaemia occurred at any point. Preoperative serum T4 concentration was 20 nmol/l (RI 10–60 nmol/l) and remained within the RI throughout the postoperative period. It reached its lowest point (12 nmol/l; RI 10–60 nmol/l) 5 days postoperatively. At this point, serum thyroid stimulating hormone (TSH) concentration was also measured using the canine TSH assay (cTSH) and found to be increased (1.78 ng/ml; RI <0.03–0.15 ng/ml). Five days later, the serum T4 concentration had increased to 13 nmol/l (RI 10–60 nmol/l) and it finally stabilised at 15 nmol/l. No clinical signs of hypothyroidism occurred at any point. Serum creatinine and phosphate concentration were also monitored postoperatively. Serum creatinine concentration (183 μ mol/l; RI <170 μ mol/l) was found to remain at the preoperative level, whereas serum

phosphate concentration returned to within the RI (1.49 mmol/l; RI 1.3–2.1 mmol/l). USG remained mildly decreased (1.031; RI >1.035).

Histopathology revealed similar findings in both masses, which consisted of polygonal chief cells with ovoid or round nuclei and lightly eosinophilic cytoplasm, water clear cells with clear and vacuolar cytoplasm, and oxyphil cells with intensively eosinophilic cytoplasm. The chief cells were arranged in solid sheets separated by fibrous stroma and formed follicle-like structures. They exhibited a neuroendocrine growth pattern, moderate anisokaryosis and anisocytosis, mild pleomorphism, increased mitotic activity (six mitoses per 10 high-power fields [HPFs] on the right side and one mitosis per 10 HPFs on the left side) and some pathological mitoses. The neoplastic cells invaded the adjacent thyroid tissue and capsule and formed a cystic tumour, combined with areas of acute haemorrhage and necrosis (Figures 5 and 6). Immunohistochemical staining was negative for calcitonin, positive for chromogranin, positive for voltage-dependent anion channel 1 in oxyphilic cells and negative for thyroglobulin (Figures 7 and 8), confirming the masses to be of neuroendocrine origin and not of thyroid origin. These findings were consistent with the diagnosis of a bilateral parathyroid carcinoma. Both tumours had been resected by marginal excision.

Discussion

Primary hyperparathyroidism is rarely reported in cats.^{1–7} It is caused by overproduction of PTH due to parathyroid gland hyperplasia or an autonomously functioning parathyroid adenoma, cystadenoma or carcinoma, with adenoma being the most common and carcinoma the rarest form.^{1,3–6,8–10} To our knowledge, this is

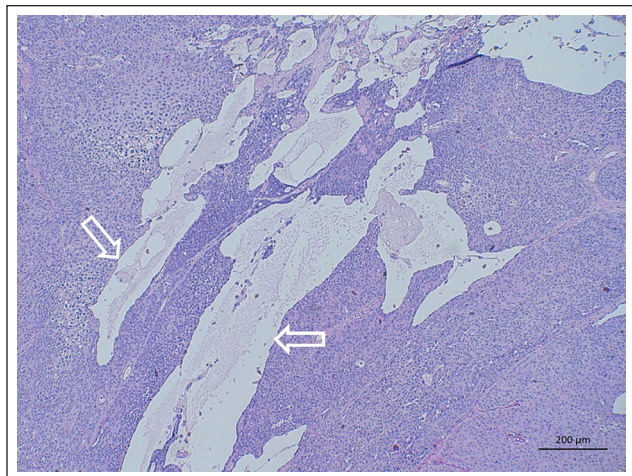


Figure 6 Histopathological image of the right-sided cystic parathyroid carcinoma (haematoxylin and eosin staining, × 50 magnification) showing cyst formation (open arrows)

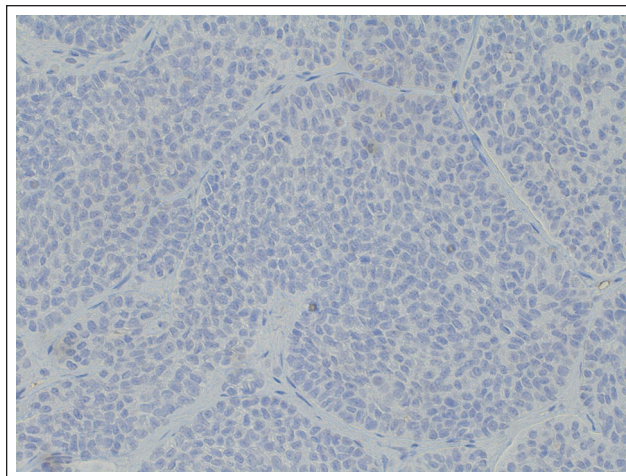


Figure 8 Histopathological image of the right-sided cystic parathyroid carcinoma (immunohistochemical staining, × 200 magnification). Immunohistochemistry showed parathyroid tumour cells were negative for thyroglobulin

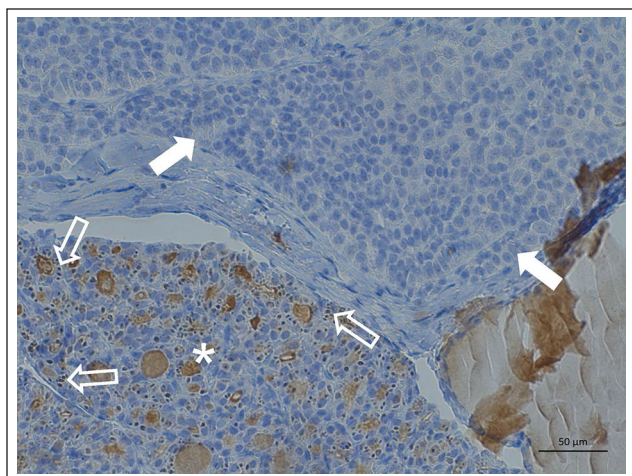


Figure 7 Histopathological image of the left-sided cystic parathyroid carcinoma (immunohistochemical staining, × 200 magnification). Immunohistochemistry showed normal thyroid tissue (*) was positive for thyroglobulin, as indicated by the small brown intracellular globules (open arrows), whereas parathyroid tumour cells (solid arrows) were negative.

the first case report of a bilateral parathyroid cystic carcinoma in a cat.

Primary hyperparathyroidism mainly affects middle-aged or older cats,¹ as was the case in this patient. No specific breed predispositions have been described.¹ Clinical signs include lethargy, anorexia, vomiting and weight loss,^{1,3,6,7,11} and 37.5% of affected cats have a palpable mass in the cervical region.¹ Despite the bilateral and malignant presentation of the disease in this case, the only reported sign was chronic vomiting.

Diagnosis of primary hyperparathyroidism is based on typical laboratory findings, including persistent hypercalcaemia with serum phosphorus concentration

being decreased or within the RI, PTH concentration being increased or within the RI, and PTHrP concentration being decreased or within the RI.^{1,4,5} It is further supported by identifying a mass in the ventral cervical region by palpation, ultrasonography or CT,^{1,5} and ultimately confirmed by histopathology.^{1-3,5,8} Ultrasonography can also aid in evaluating regional lymph nodes, ruling out other causes for the non-specific clinical signs, and detecting changes secondary to the hypercalcaemia such as soft tissue mineralisation, urinary calculi and renal degeneration.^{1,2} In this case, the laboratory results and the diagnostic imaging findings were consistent with primary hyperparathyroidism, with no evidence of metastasis or significant soft tissue mineralisation. Ectopic parathyroid tissue was not identified but scintigraphy would have been required to exclude it. The renal atrophy, mild azotaemia and mildly decreased USG were most likely related to concurrent chronic kidney disease (CKD).

Preoperative distinction between a thyroid and a parathyroid lesion can be challenging even with ultrasonography, CT and FNA,^{3,6-8} which was also the case in this cat. In many of the previously reported cases, exploratory surgery of the ventral neck had been performed in order to confirm the diagnosis.^{1,2,6,11} However, intra-operative identification of all hyper-functional tissue can be difficult, especially in the presence of non-functional thyroid and parathyroid nodules.^{8,12} Indeed, in a recent study, several cats needed a second operation owing to persistent hypercalcaemia.¹

Many of the functional parathyroid masses reported have been cystic,^{5,8,9} and the cysts of functional parathyroid masses typically contain a much higher concentration of PTH compared with that of serum.^{3,8,9} Measuring PTH concentration in cystic fluid preoperatively is recommended to confirm the hormonal activity of the mass.^{5,8,9}

In this case, it turned out to be a valuable diagnostic procedure. Owing to the small size of the parathyroid cysts, the aspirated fluid samples needed to be diluted with sterile saline to achieve the required volume for PTH measurement, which carries a risk of dilution error. The authors therefore recommend this only be performed by appropriately trained laboratory personnel.

Surgical excision of the affected parathyroid glands is currently the most commonly used treatment for primary hyperparathyroidism in cats.¹ Ethanol ablation has recently been described as a non-invasive alternative.³ However, it does not allow histopathological diagnosis, and has been reported to cause adverse effects such as dysphonia, Horner's syndrome and laryngeal paralysis when used for the treatment of thyroid nodules in cats.¹³ In addition, ethanol ablation has only been able to provide transient euthyroidism when used for the treatment of bilateral thyroid nodules, and is therefore not recommended in bilateral cases.¹³

Possible complications related to parathyroidectomy in cats include iatrogenic trauma to the recurrent laryngeal nerve causing acute dyspnoea, and iatrogenic hypoparathyroidism causing hypocalcaemia, although clinical signs related to the latter, such as tetany, facial itching and weakness, are rarely reported in cats.^{1,3,5,8,9,11} However, monitoring iCa concentration 1–6 days postoperatively is recommended.^{1,5,8} Singh et al¹ reported that the median time for hypocalcaemia to develop was 36 h postoperatively and calcium supplementation was initiated if iCa concentration decreased below 1.30 mmol/l. In the present case, iCa concentration reached its lowest point of 0.90 mmol/l (RI 1.15–1.40 mmol/l) 19 days postoperatively but, as there were no clinical signs of hypocalcaemia, calcium supplementation was not initiated in order to maintain the stimulus for the cat's endogenous PTH secretion.¹⁴ By the next follow-up appointment 6 days later, iCa concentration had returned to within the RI. Achieving normocalcaemia may have been due to successful preservation of functional parathyroid tissue, but the existence of ectopic parathyroid tissue cannot be ruled out, and alternative mechanisms such as alterations in renal calcium metabolism may also have contributed to the process.¹⁵

Possible complications related to thyroidectomy in cats include iatrogenic hypothyroidism and worsening azotaemia due to decreased glomerular filtration rate. Although there was a mild postoperative decrease in serum T4 concentration, it did not decrease below the lower end of the RI, nor were there any clinical signs of hypothyroidism. This is most likely due to the left thyroid gland being partially preserved at surgery, although the existence of ectopic thyroid tissue cannot be ruled out. As the development of subclinical iatrogenic hypothyroidism was anticipated when the serum

T4 concentration reached its lowest point, serum cTSH concentration was measured using the canine assay, which, in the absence of a commercial feline TSH assay, has been shown to be useful in cats.^{16,17} No levothyroxine supplementation was initiated in order to stimulate the remaining thyroid gland to restore the cat's endogenous T4 production.¹¹

Deteriorating CKD does not seem to be a commonly reported sequela after thyroidectomy and parathyroidectomy in euthyroid cats. In a case report describing worsening azotaemia postoperatively, the process was completely reversible, with the serum creatinine concentration returning to its preoperative level in 2 months.⁶ In the present case, serum creatinine concentration remained at the preoperative level.

Histopathological characteristics of parathyroid carcinomas in cats include early invasion into the thyroid tissue and the formation of multiple cysts.¹⁸ Some carcinomas may exhibit areas of haemorrhage and necrosis, and the mitotic count or the degree of pleomorphism may be increased.¹⁸ Distant metastases, however, are uncommon.¹⁸ In the present case, the diagnosis was based on identifying these histopathological characteristics.

In human medicine, parathyroid neoplasms with some histopathological features of carcinomas, but unequivocal evidence of invasive growth, are known as atypical parathyroid adenomas.¹⁹ As such, they represent a challenge for the histopathological diagnosis of parathyroid carcinoma. To our knowledge, no standardised diagnostic criteria for atypical parathyroid adenomas in cats have been published.

The prognosis for surgically treated primary hyperparathyroidism is good. Singh et al¹ reported that 1/7 cats diagnosed with a unilateral parathyroid carcinoma developed local recurrence 837 days postoperatively and 2/7 cats metastasised to regional lymph nodes, whereas none had evidence of pulmonary metastasis. According to the same study, malignancy of the tumour was not associated with a shorter mean survival time, but owing to the small sample size these results must be interpreted cautiously.¹ In the present case, the cat was reported to feel well at a follow-up appointment 5 months postoperatively and no signs of local recurrence or metastatic disease were detected.

Conclusions

To our knowledge, this is the first report to describe a rare case of bilateral parathyroid cystic carcinoma in a cat. Measuring PTH concentration in the cystic fluid of a suspected parathyroid mass preoperatively is a useful tool to confirm hormonal activity of the mass.

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.

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 was therefore not specifically required for publication in *JFMS*.

Informed consent Informed consent (either verbal or written) was obtained from the owner or legal custodian of all 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.

ORCID iD Susanne Kilpinen  <https://orcid.org/0000-0001-8786-8504>

References

- 1 Singh A, Giuffrida MA, Thomson CB, et al. **Perioperative characteristics, histological diagnosis, and outcome in cats undergoing surgical treatment of primary hyperparathyroidism.** *Vet Surg* 2019; 48: 367–374.
- 2 Sueda MT and Stefanacci JD. **Ultrasound evaluation of the parathyroid glands in two hypercalcemic cats.** *Vet Radiol Ultrasound* 2000; 41: 448–451.
- 3 Riehl V, Hartmann A, Rohrberg A, et al. **Percutaneous ultrasound-guided ethanol ablation for treatment of primary hyperparathyroidism in a cat.** *JFMS Open Rep* 2019; 5. DOI: 10.1177/2055116919860276.
- 4 Savary KC, Price GS and Vaden SL. **Hypercalcemia in cats: a retrospective study of 71 cases (1991–1997).** *J Vet Intern Med* 2000; 14: 184–189.
- 5 Cavana P, Vittone V, Capucchio MT, et al. **Parathyroid adenocarcinoma in a nephropathic Persian cat.** *J Feline Med Surg* 2006; 8: 340–344.
- 6 Faucher MR, Freiche V, Bongrand Y, et al. **Primary hyperparathyroidism caused by a parathyroid carcinoma in a 16-year-old male neutered cat with concurrent chronic kidney disease.** *Vet Q* 2014; 34: 37–40.
- 7 den Hertog E, Goossens MM, van der Linde-Sipman JS, et al. **Primary hyperparathyroidism in two cats.** *Vet Q* 1997; 19: 81–84.
- 8 Lamoureux A, Fournet A, Hahn HM, et al. **Primary hyperparathyroidism due to a cystic parathyroid adenoma in a cat.** *Open Vet J* 2019; 9: 109–113.
- 9 Phillips DE, Radlinsky MG, Fischer JR, et al. **Cystic thyroid and parathyroid lesions in cats.** *J Am Anim Hosp Assoc* 2003; 39: 349–354.
- 10 Marquez GA, Klausner JS and Osborne CA. **Calcium oxalate urolithiasis in a cat with a functional parathyroid adenocarcinoma.** *J Am Vet Med Assoc* 1995; 206: 817–819.
- 11 Kaplan E. **Primary hyperparathyroidism and concurrent hyperthyroidism in a cat.** *Can Vet J* 2002; 43: 117–119.
- 12 Norsworthy GD, Adams VJ, McElhaney MR, et al. **Palpable thyroid and parathyroid nodules in asymptomatic cats.** *J Feline Med Surg* 2002; 4: 145–151.
- 13 Wells AL, Long CD, Hornof WJ, et al. **Use of percutaneous ethanol injection for treatment of bilateral hyperplastic thyroid nodules in cats.** *J Am Vet Med Assoc* 2001; 218: 1293–1297.
- 14 Barber PJ. **Disorders of the parathyroid glands.** *J Feline Med Surg* 2004; 6: 259–269.
- 15 Padgett SL, Tobias KM, Leathers CW, et al. **Efficacy of parathyroid gland autotransplantation in maintaining serum calcium concentrations after bilateral thyroparathyroidectomy in cats.** *J Am Anim Hosp Assoc* 1998; 34: 219–224.
- 16 Wakeling J. **Use of thyroid stimulating hormone (TSH) in cats.** *Can Vet J* 2010; 51: 33–34.
- 17 Peterson ME, Guterl JN, Nichols R, et al. **Evaluation of serum thyroid-stimulating hormone concentration as a diagnostic test for hyperthyroidism in cats.** *J Vet Intern Med* 2015; 29: 1327–1334.
- 18 Rosol TJ and Meuten DJ. **Tumors of the endocrine glands.** In: Meuten DJ (ed). *Tumors in domestic animals*. 5th ed. Ames, IA: John Wiley & Sons, 2017, pp 809–815.
- 19 Cetani F, Marcocci C, Torregrossa L, et al. **Atypical parathyroid adenomas: challenging lesions in the differential diagnosis of endocrine tumors.** *Endocr Relat Cancer* 2019; 26: 441–464.