Spontaneous proliferative and neoplastic lesions in thyroid and parathyroid glands of non-domestic felids

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Running title: Proliferative thyroid and parathyroid lesions in exotic cats
Abstract. Based on microscopic and immunohistochemical characterization, we documented spontaneous proliferative and neoplastic lesions in the thyroid and parathyroid glands of non-domestic felids. Ten animals (4 leopards, 3 tigers, and 3 cougars), all with a previous diagnosis of thyroid neoplasia were identified from the University of Tennessee College of Veterinary Medicine (UTCVM) case database. The mean age of affected animals was 15.9 years. Twelve neoplasms were identified; 2 animals had 2 concurrent neoplasms. After immunohistochemical characterization using a panel of chromogranin A, thyroglobulin, and calcitonin, 7 of the former thyroid neoplasms were diagnosed as thyroid adenomas, 1 was diagnosed as a thyroid carcinoma, and 4 were diagnosed as parathyroid adenomas. No thyroid medullary neoplasms (C cell tumors) were diagnosed in the current study. Most of the diagnosed neoplasms were benign (11/12 [92%]), and metastasis was not documented in the single carcinoma. Only 2 animals were suspected to have functional neoplasms (1 thyroid adenoma and 1 parathyroid adenoma), based on associated tissue lesions or serum biochemistry. Other documented lesions in the thyroid and parathyroid glands included thyroid nodular hyperplasia (n = 7), parathyroid hyperplasia associated with chronic renal disease (n = 2), a thyroid abscess, and a branchial cyst. Parathyroid adenomas were more commonly diagnosed than expected in comparison to domestic cats. An immunohistochemistry panel for thyroglobulin, calcitonin, and chromogranin A can be used to differentiate neoplasms of thyroid from parathyroid origin in non-domestic felids.

Key words: exotic cats; felids; immunohistochemistry; neoplasia; parathyroid; thyroid

Introduction
Thyroid nodular hyperplasia and thyroid follicular adenomas are common in older domestic cats. Two recent case reports document functional and non-functional thyroid carcinomas in captive non-domestic felids, including a cougar (*Felis concolor*) and multiple leopards (*Panthera pardus*). In a study at the Philadelphia Zoological Gardens that spanned 55 years, the most commonly documented neoplasms of carnivores were of the endocrine organs. Thyroid adenomas were documented in multiple non-domestic felids, and thyroid carcinomas were documented in a leopard, lion (*Panthera leo*), puma (*Puma concolor*), and Sumatran tiger (*Panthera tigris*). Both the benign and malignant neoplasms were proposed to be secondary to an iodine-deficient diet. In a more recent study of neoplasia in non-domestic felids at the Knoxville Zoological Gardens that spanned 24 years, neoplasms of the endocrine organs were the second most commonly reported, following neoplasms of the integument. Of these endocrine neoplasms, 80% were associated with the thyroid gland, suggesting that proliferative lesions in non-domestic felids occur with some frequency.

In this retrospective study, we describe microscopic characteristics and immunohistochemical staining patterns of previously diagnosed thyroid neoplasms. The primary goal of this study was to use immunohistochemistry to definitively characterize these neoplasms as either thyroid or parathyroid in origin. Additionally, other thyroid lesions and lesions in the associated parathyroid glands are described. The final goal of the study was to compare non-domestic felid thyroid lesions to those seen in domestic cats.

**Materials and methods**

Autopsy reports on non-domestic felids filed by the Pathology Service at the University of Tennessee’s Veterinary Medical Center were reviewed for a diagnosis of thyroid neoplasia or other lesions. Species, sex, age at death, previous and final diagnoses, and cause of death or
euthanasia were recorded for each case (Table 1). Information about clinical pathology, when
performed, was also obtained from these animals’ medical records for the 2 most recent times
(Table 1).

Thyroid and parathyroid tissues were fixed in 10% buffered formalin, sectioned at 5 µm, and
stained with hematoxylin and eosin. All stained sections were reviewed by a board-certified
pathologist (SJN) and a pathology resident (JPP).

Chromogranin A, a thyroglobulin, b and calcitonin c antibodies were optimized using thyroid,
parathyroid, and archived adrenal medullary tissue from both non-domestic felids and domestic
cats. These same tissues not receiving the primary antibodies in each case served as negative
controls. Non-neoplastic thyroid follicular cells, C cells, and chief cells within the individual
cases served as internal positive controls. All thyroid, parathyroid, and adrenal gland tissues were
cut at 5 µm, placed on charged slides, air dried, and heated at 60°C for 15 min. All slides were
deparaffinized using xylene and then rehydrated through graded ethanols to deionized water. For
chromogranin A slides, heat-induced epitope retrieval was done with citrate buffer at pH 6 in a
steamer at 95°C for 20 min. Thyroglobulin slides had no antigen retrieval performed. For
calcitonin slides, enzyme-induced antigen retrieval d was done at room temperature for 5 min. All
slides were rinsed in deionized water and soaked in Tris buffered saline–Tween (TBST) for 10
min before being placed into an autostainer e at room temperature and rinsed with TBST between
steps. A 3% hydrogen peroxide block was applied for 5 min to all slides. A serum-free protein
block was applied for 20 min to the chromogranin A slides, for 30 min to the thyroglobulin
slides, and for 5 min to the calcitonin slides. Chromogranin A was applied for 90 min at a 1:200
dilution; thyroglobulin was applied for 20 min at a 1:60,000 dilution; and calcitonin was applied
for 30 min at a 1:500 dilution. The labeled polymer anti-mouse f for chromogranin A slides and
anti-rabbit\textsuperscript{g} for thyroglobulin and calcitonin slides (commercial horseradish-peroxidase system) were applied for 30 min, and DAB (3,3’diaminobenzidine tetrahydrochloride)\textsuperscript{h} was applied as the chromogen for 10 min to all slides. All slides were then rinsed with deionized water, stained for 5 sec in hematoxylin, blued in ammonia water, dehydrated through ethanol, cleared with xylene, and coverslipped. Diagnosis was based on criteria outlined in Table 2.

**Results**

Ninety accessions were reviewed, and 12 non-domestic felids were identified with thyroid neoplasia, 2 animals were excluded because tissues were either not available or too autolyzed for inclusion in the study, reducing the number of study animals to 10. Seven of these neoplasms in 5 non-domestic felids were published previously \textsuperscript{14} but are further characterized in the current study; 5 additional animals were included from the autopsy reports. The ages of 1 tiger and 1 leopard were unknown. The youngest and oldest cases, with known ages at death, were a 13-year-old leopard and a 22-year-old tiger, respectively. The mean age at death for all non-domestic felids in the current study was 15.9 years.

Twelve neoplasms were originally diagnosed as thyroid neoplasms, with 2 animals having 2 concurrent neoplasms. Following immunohistochemical characterization in conjunction with the diagnostic criteria described (Table 2), 7 of these neoplasms were diagnosed as thyroid adenomas (Fig. 1C, D), 1 as a thyroid carcinoma (Fig. 1E, F), and 4 as parathyroid adenomas (Fig. 1A, B). No thyroid medullary neoplasms (C cell tumors) were identified in the current study. Antibodies for calcitonin and thyroglobulin were able to be optimized for use in non-domestic felids, but an anti-PTH antibody was unable to be utilized for confirmatory diagnosis of parathyroid neoplasms in our laboratory, despite use of multiple protocols and several commercially available reagents. Most (11/12, 92\%) of the diagnosed neoplasms were benign,
and metastasis was not recorded in any reports, including the final autopsy report of the animal with the thyroid carcinoma. Other lesions in these 10 felid thyroid glands and parathyroid glands included thyroid nodular hyperplasia with follicular cysts \((n = 7)\), parathyroid hyperplasia associated with chronic renal disease \((n = 2)\), a thyroid abscess, and a branchial cyst.

Clinical pathology results were available from 2 animals with parathyroid adenomas (Table 1): 1 leopard with a parathyroid adenoma, and 1 tiger with both a parathyroid adenoma and a thyroid adenoma. The leopard had an increased calcium concentration \((3.07 \text{ mmol/L [12.3 mg/dL]}; \text{ reference interval} = 2.20-2.89 \text{ mmol/L [8.8–11.6 mg/dL]}^{19})\) at 1 sampling, but calcium concentrations decreased to within the normal reference interval in subsequent plasma samples. The tiger had no biochemical changes suggestive of thyroid or parathyroid disease. Parathyroid hormone (PTH) levels were not available for any of the study animals. Triidothyronine (T3), thyroxine (T4), and thyroid-stimulating hormone (TSH) levels were not available antemortem for any of the study animals, and plasma biochemical abnormalities that would be consistent with, but not specific for, clinical hyperthyroidism (such as elevated alkaline phosphatase [ALP] activity) were not observed in any felid for which clinical pathology testing was performed \((n = 5; \text{ Table 1})\). In addition, for animals with thyroid neoplasms, body condition varied from emaciated to obese. Iodine levels were not available for any of the study animals.

Hyperthyroidism was considered in the snow leopard with a thyroid adenoma because of concurrent hypertrophic cardiomyopathy (a lesion documented in domestic cats with hyperthyroidism) and hyperphosphatemia, without primary renal tubular disease, but was not confirmed.

The causes of death or euthanasia varied and included renal disease \((n = 3)\), renal disease and interstitial pneumonia \((n = 1)\), intervertebral disc disease \((n = 2)\), Wallerian degeneration of the
spinal cord \((n=1)\), degenerative joint disease \((n=1)\), necrotizing pancreatitis and disseminated intravascular coagulation \((n=1)\), and metastatic fibrosarcoma \((n=1)\). Thyroid or parathyroid neoplasms were not considered to contribute to the cause of death or euthanasia in any of the cases. Additional lesions found at autopsy that were potentially related to the thyroid lesions included hypertrophic cardiomyopathy in a snow leopard with bilateral thyroid adenomas and a pancreatic islet cell tumor in a tiger with a thyroid adenoma and parathyroid gland hyperplasia.

**Discussion**

Thyroid neoplasms were more common than parathyroid neoplasms in the current study; the parathyroid neoplasms were diagnosed only following immunohistochemical characterization. However, parathyroid neoplasms were more commonly diagnosed than expected, compared to domestic cats. A leopard with a parathyroid adenoma had a 1-time increased plasma calcium concentration, as well as anorexia, which were interpreted as non-specific findings potentially associated with a functional neoplasm. Neoplasms in the other 3 animals were suspected to be non-functional.

Bilateral parathyroid gland hyperplasia (secondary hyperparathyroidism) associated with chronic renal failure is commonly reported in domestic cats. While renal failure was not confirmed in our cases, two of the felids in the current study had findings supportive of significant renal disease and possible associated secondary hyperparathyroidism, 1 based on laboratory findings of azotemia and 1 with an autopsy finding of interstitial nephritis. Parathyroid gland hyperplasia can also occur in association with hyperthyroidism. The thyroid neoplasms diagnosed in these 2 animals were suspected, but not confirmed, to be non-functional.

Domestic cats with thyroid neoplasms are typically geriatric, with a mean age of 12.4 years at diagnosis of adenomas and 15.8 years for diagnosis of carcinomas. The mean age at diagnosis
for the non-domestic felids in the present study, 15.9 years, was similar to domestic cats. Thyroid

glands can develop hyperplastic and neoplastic lesions from both the thyroid follicular cells and

the surrounding C cells (parafollicular cells). Domestic cats most commonly develop either

thyroid nodular hyperplasia, with bilateral involvement in up to 70% of cases, or follicular

adenomas, both which can result in hyperthyroidism.\textsuperscript{1,3,15} Seven non-domestic felids had foci

consistent with thyroid nodular hyperplasia, which, to our knowledge, has not been described

previously in non-domestic felids. Unlike domestic cats, these hyperplastic lesions were

suspected to be non-functional, based on available supporting laboratory results, but this

suspicion cannot be confirmed without evaluation of T3 or T4 values. Because of the one case of

concurrent hypertrophic cardiomyopathy, the possibility of functionality requires further study.

All of the non-domestic felids in this study were captive, and previous reports have implicated an

iodine-deficient diet in the development of thyroid neoplasms in captive exotic cats.\textsuperscript{9} Neither

blood iodine levels nor dietary iodine levels were measured in this study, so it is unclear if

iodine-deficiency played a role in thyroid neoplasm development in these exotic cats.

Thyroid follicular adenomas are more common than follicular carcinomas in domestic cats,\textsuperscript{1,3}

and similarly, only one thyroid follicular carcinoma was diagnosed in a tiger in the current study.

Thyroid follicular carcinomas with metastases have been described in a tiger, a puma, and a

leopard,\textsuperscript{7} but metastases were not recorded in the autopsy report for the tiger included in the

current study. In domestic cats, thyroid follicular carcinomas metastasize <50% of the time, most

commonly to the regional lymph nodes rather than lungs.\textsuperscript{1,2,15} No medullary (C cell) thyroid

neoplasms were diagnosed in the study, which is similar to the case in domestic cats, in which

these neoplasms are rare.\textsuperscript{2}
A single tiger had lesions consistent with multiple endocrine neoplasia (MEN) and included bilateral parathyroid gland hyperplasia, a thyroid follicular adenoma, and a pancreatic islet cell carcinoma. In humans,\textsuperscript{17} MEN-1 is associated with a mutation in the \textit{menin} gene that results in lesions in parathyroids and endocrine pancreas with subtypes that can lead to additional lesions in the thyroids,\textsuperscript{17} as in this tiger. A MEN-1-like syndrome has been reported in 2 domestic shorthair cats, but examination of the \textit{menin} gene for mutations in those cats was unsuccessful.\textsuperscript{17} We were not able to evaluate the tiger in the present study for \textit{menin} gene mutations.

All neoplasms (n=12) included in the current study were originally diagnosed as thyroid neoplasms. Following immunohistochemical characterization, 4 were reclassified as parathyroid adenomas (Table 1). Immunohistochemistry has not been used in non-domestic felids to further characterize these neoplasms, but has been used in domestic cats to differentiate tumors arising from thyroid follicular cells (thyroglobulin), C cells (calcitonin), and chief cells (parathyroid hormone) (Chaitman SJ, et al. Immunohistochemical staining of thyroglobulin in thyroid glands of normal cats, hyperthyroid cats, and cats with euthyroxinemia. Proc 18th Am Coll Vet Internal Med Meeting; 2000 May 25–28; Seattle, WA).\textsuperscript{2,13} Both medullary thyroid tumors (C cell tumors) and parathyroid gland tumors can be immunoreactive for chromogranin A and synaptophysin.\textsuperscript{2,5} The single thyroid carcinoma included in our study had a few neoplastic cells (<5\%) that stained positively with thyroglobulin, and poorly differentiated thyroid follicular carcinomas, as in this case, have been reported to be negative for thyroglobulin.\textsuperscript{12,16} Chromogranin A was used to confirm neoplasms of parathyroid based on its previous use in dogs\textsuperscript{5} and its reported conservation between species.\textsuperscript{2} Immunohistochemical staining with chromogranin A was observed to be most intense in leopards and less intense in tigers, suggesting a species difference in immunoreactivity; one tiger had poor immunohistochemical
staining with both thyroglobulin and chromogranin A. Chromogranin A staining was most intense in hyperplastic parathyroid lesions. Staining differences of PTH and chromogranin A in normal, hyperplastic, and neoplastic parathyroid lesions have been documented.\textsuperscript{5,18,20}

Parathyroid neoplasms were more common than expected in this population of non-domestic felids, when compared to domestic cats, but an immunohistochemistry panel may be required for accurate diagnosis. Most of the thyroid neoplasms and all of the parathyroid neoplasms in these non-domestic felids were benign. Most of the thyroid and parathyroid neoplasms were suspected to be non-functional based on the available laboratory results, clinical history, and recorded lesions; however, without evaluation of more specific serum biochemistry parameters, including TSH, T3, T4, and PTH, this suspicion cannot be confirmed. For the non-domestic felid cases in this study, spindle cell morphology of a portion of the neoplastic cells in parathyroid gland tumors that was then confirmed by immunohistochemistry was one of the most discriminating features for differentiation of origin by microscopic examination. Chromogranin A, thyroglobulin, and calcitonin can be used as a panel in non-domestic felids to distinguish parathyroid, thyroid follicular, and thyroid medullary origin of neoplasms.

Sources and manufacturers


b. Polyclonal rabbit thyroglobulin antibody, Dako North America Inc., Carpinteria, CA.

c. Polyclonal rabbit calcitonin antibody, Dako North America Inc., Carpinteria, CA.

d. Proteinase K, Dako North America Inc., Carpinteria, CA.

e. Autostainer S3400, Dako North America Inc., Carpinteria, CA.

f. EnVision + System HRP Anti-mouse, Dako North America Inc., Carpinteria, CA.
g. EnVision + System HRP Anti-rabbit, Dako North America Inc., Carpinteria, CA.

h. Dako North America Inc., Carpinteria, CA.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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References


Table 1. Signalment, descriptive diagnosis, relevant clinical chemistry findings, and pertinent cause of death or euthanasia in 10 non-domestic felids with thyroid or parathyroid neoplasia

<table>
<thead>
<tr>
<th>Species</th>
<th>Age at death (years)</th>
<th>Sex</th>
<th>Previous diagnosis</th>
<th>Final diagnosis</th>
<th>Change in diagnosis</th>
<th>Urea (mmol/L)</th>
<th>Creatinine (µmol/L)</th>
<th>Calcium (mmol/L)</th>
<th>PO4 (mmol/L)</th>
<th>Cause of death or euthanasia</th>
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<tr>
<td>Leopard</td>
<td>13</td>
<td>F</td>
<td>Multiple thyroid adenoma, thyroid follicular nodular adenomas with follicular atrophy</td>
<td>Parathyroid adenoma, thyroid follicular nodular adenomas with follicular cysts</td>
<td>Yes</td>
<td>Not available (NA)</td>
<td>Degenerative joint disease</td>
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<td></td>
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<tr>
<td>Black Leopard</td>
<td>Geriatric</td>
<td>F</td>
<td>Thyroid</td>
<td>Parathyroid</td>
<td>Yes</td>
<td>15 (42), 124 (1.4), 3.07</td>
<td>628 (7.1), (12.3), (4.5)</td>
<td>Pyelitis with renal papillary</td>
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*Relevant clinical chemistry findings:*

- Urea
- Creatinine
- Calcium
- PO4
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<tr>
<th></th>
<th>Heart Rate</th>
<th>Arrival Time</th>
<th>Stay Duration</th>
<th>Diagnosis</th>
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<td>19 M</td>
<td>Thyroid</td>
<td>Parathyroid</td>
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<td></td>
<td></td>
<td>follicular</td>
<td>adenoma with</td>
<td>cystic, multiple degeneration, thyroid nodular follicular cysts</td>
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<td></td>
<td></td>
<td></td>
<td>follicles</td>
<td></td>
</tr>
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<td>Snow leopard</td>
<td>16 F</td>
<td>Multiple</td>
<td>Multiple thyroid</td>
<td>No, 11.8, 212 (2.4), 2.10, 1.10 Disseminated intravascular coagulation,</td>
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<td></td>
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<td>thyroid</td>
<td>follicular</td>
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<td></td>
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<td>adenomas</td>
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necrosis, interstitial pneumonia, chronic, ankylosing spondylosis
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<td>Cougar</td>
<td>17</td>
<td>M</td>
<td>Multiple</td>
<td>Thyroid</td>
<td>15(42),</td>
<td>301 (3.4),</td>
<td>2.22</td>
<td>2.23</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>thyroid follicular</td>
<td>15.4</td>
<td>274 (3.1)</td>
<td>(8.9),</td>
<td>(6.9),</td>
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<td></td>
<td></td>
<td></td>
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<td>(43)</td>
<td>2.59</td>
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<td></td>
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<td>adenomas</td>
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<td>(10.4)</td>
<td>(4.4)</td>
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<tr>
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<td>17</td>
<td>F</td>
<td>Multiple</td>
<td>Unilateral</td>
<td>16.1</td>
<td>336 (3.8),</td>
<td>2.62</td>
<td>1.49</td>
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<td>11.1</td>
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<td>adenomas, bilateral thyroid</td>
<td>(31)</td>
<td>(9.6)</td>
<td>(4.3)</td>
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<td></td>
<td></td>
<td></td>
<td>multifocal nodular thyroid nodular hyperplasia and</td>
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<tr>
<td>Cougar</td>
<td>18</td>
<td>M</td>
<td>Bilateral</td>
<td>Bilateral</td>
<td>38.9</td>
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<td></td>
<td></td>
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<td>parathyroid parathyroid</td>
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16
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<tr>
<th></th>
<th>gland</th>
<th>52.5</th>
<th>(9.3)</th>
<th>2.68</th>
<th>interstitial</th>
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<td></td>
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<tr>
<td>Tiger 15 M Multiple Parathyroid Yes</td>
<td>41.8</td>
<td>159 (1.8)</td>
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<td>NA</td>
<td>Chronic glomerulonephritis</td>
</tr>
<tr>
<td>Tiger</td>
<td>Age</td>
<td>Sex</td>
<td>Thyroid</td>
<td>Parathyroid</td>
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<tr>
<td>Adult</td>
<td>MC</td>
<td>M</td>
<td>Thyroid follicular</td>
<td>Thyroid follicular</td>
<td>No</td>
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<td></td>
<td></td>
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<td>carcinoma</td>
<td>carcinoma</td>
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<tr>
<td>Tiger</td>
<td>22</td>
<td>M</td>
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<td>Parathyroid hyperplasia, adenoma, thyroid follicular</td>
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<td></td>
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<td></td>
<td></td>
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<td>hyperplasia nodular hyperplasia and follicular cysts</td>
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* RR = Within reference intervals: urea = 6.1–12.5 mmol/L (17–35 mg/dL), creatinine = 62–186 µmol/L (0.7–2.1 mg/dL), calcium = 2.05–2.87 mmol/L (8.2–11.5 mg/dL), phosphorus (PO4) = 0.84–2.07 mmol/L (2.6-6.4 mg/dL). All animals were within reference interval for alkaline phosphatase: 15–96 IU (15–96 U/L).

† F = female; M = male; MC = male castrated.
Table 2. Diagnostic criteria for lesions included in the study: thyroid nodular hyperplasia, thyroid follicular adenoma, thyroid carcinoma, parathyroid hyperplasia, and parathyroid gland adenoma.

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Thyroglobulin</th>
<th>Calcitonin</th>
<th>Chromogranin A</th>
<th>Microscopic features</th>
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<tbody>
<tr>
<td>Nodular hyperplasia</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Microscopic (not documented on gross exam or &lt;1.5 mm on microscopic exam); minimally compressive; focal or multifocal</td>
</tr>
<tr>
<td>Thyroid follicular adenoma</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Macroscopic (documented on gross exam or &gt;1.5 mm on microscopic examination); compressive; +/- encapsulated</td>
</tr>
<tr>
<td>Thyroid carcinoma</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>Increased mitotic rate (&gt; 10 mitoses per 10 high power fields); infiltrative; increased nuclear pleomorphism</td>
</tr>
<tr>
<td>Parathyroid gland hyperplasia</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>Minimally compressive; unencapsulated; 2 or more parathyroids enlarged</td>
</tr>
<tr>
<td>Parathyroid gland adenoma</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+/- Encapsulated; compressive; single enlarged parathyroid; spindle morphology of some neoplastic cells</td>
</tr>
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Figure 1. Histopathology and immunohistochemistry of parathyroid and thyroid neoplasms in non-domestic felids. (A, B) Black leopard, parathyroid adenoma. (A) Spindle cell morphology of a portion of the neoplastic cells. Hematoxylin and eosin (H&E). Bar = 20 μm. (B) Palisading of neoplastic cells with positive cytoplasmic staining. Chromogranin A. Bar = 20 μm. (C, D) Snow leopard, thyroid follicular adenoma. (C) Neoplastic cells forming follicles containing colloid. H&E. Bar = 20 μm. (D) Positive cytoplasmic staining of cells and colloid. Thyroglobulin. Bar = 20 μm. (E, F) Tiger, thyroid follicular carcinoma. (E) Sheets of neoplastic polygonal cells with abundant lightly vacuolated cytoplasm and central round nuclei, multiple mitoses. H&E. Bar = 20 μm. (F) Rare positive cytoplasmic staining of follicular structures with remaining negative neoplastic cells. Thyroglobulin. Bar = 20 μm. Inset: tiger thyroid follicular carcinoma, adjacent normal thyroid, positive cytoplasmic staining of non-neoplastic C cells, negative surrounding non-neoplastic thyroid cells. Calcitonin. Bar = 20 μm.