

# A Mass in the Ventral Neck of a Hypercalcemic Dog

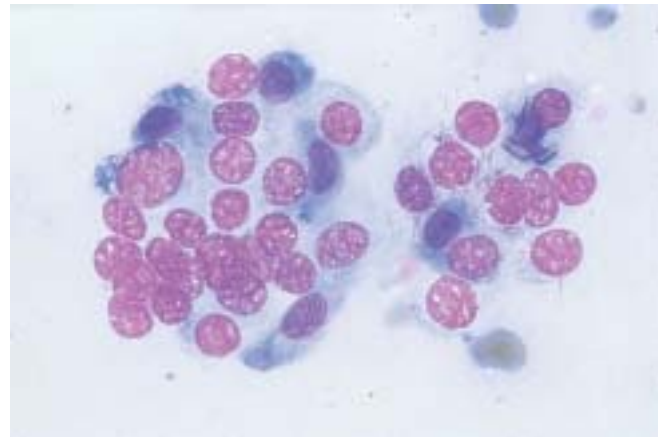
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## Case Presentation

An 11-year-old intact male Dalmatian was referred to the Veterinary Medical Teaching Hospital at the University of Florida, Gainesville, Fla, with a history of disorientation, ataxia, and vomiting for the past 36 hours. The dog was primarily housed indoors, but occasionally had unsupervised outdoor activity. Vaccinations were current and a recent heartworm test was negative. The dog received regular heartworm and flea preventives. Upon presentation to the referring veterinarian, a CBC and chemistry panel were performed. Results of the CBC were within reference limits. Increases were observed in serum total calcium (23.0 mg/dL; reference range, 8.6-11.2 mg/dL), BUN (40 mg/dL; reference range, 6-28 mg/dL), total protein (8.4 g/dL; reference range, 5.6-8.0 g/dL), albumin (4.2 g/dL; reference range, 2.5-4.0 g/dL), and globulins (4.2 g/dL; reference range, 2.0-3.8 g/dL) concentrations, and in alkaline phosphatase (ALP, 276 IU/L; reference range, 20-200 IU/L), and alanine aminotransferase (64 IU/L; reference range, 0-57 IU/L) activities. Chloride concentration was below the reference range at 104 mEq/L (reference range, 105-115 mEq/L). The referring veterinarian initiated intravenous saline diuresis and referred the patient for further evaluation.

Physical examination findings upon presentation to the Teaching Hospital included generalized weakness and occasional fine tremors. Vital signs were within reference limits. Results of thoracic auscultation were normal. Abdominal palpation and rectal examination were unremarkable. Neurologic examination results and reflexes were within reference limits.

Initial findings in the CBC included mature neutrophilia (18,160 cells/ $\mu$ L; reference range, 3000-11,500 cells/ $\mu$ L) and monocytosis (2040 cells/ $\mu$ L; reference range, 150-1350 cells/ $\mu$ L). Biochemical abnormalities included increases in total calcium (16.6 mg/dL; reference range, 9.3-11.3 mg/dL), ionized calcium (2.29 mmol/L; reference range, 1.12-1.40 mmol/L), BUN (55 mg/dL; reference range, 6-26 mg/dL), and creatinine (3.3



**Figure 1.** Tissue impression smear of a ventral neck mass from a dog. Note the distinct eosinophilic needle-like structures in the cytoplasm of some cells. Wright's stain,  $\times 250$ .

mg/dL; reference range, 0.3-1.6 mg/dL) concentrations, and in ALP (211 IU/L; reference range, 20-126 IU/L), and aspartate aminotransferase (88 IU/L; reference range, 0-57 IU/L) activities.

The patient's profound hypercalcemia was considered to be of primary importance. Results of radioimmunoassays (Animal Health Diagnostic Laboratory, Michigan State University, East Lansing, Mich) for serum parathormone (PTH; 7.3 pmol/L; reference range, 2.0-13.0 pmol/L) and parathormone-related protein (PTHrP; undetectable; reference range, <0.2 pmol/L) were within reference limits. Serum 25-hydroxy vitamin D concentration was low (77 nmol/L; reference range, 82-285 nmol/L). Results of bone marrow aspiration cytology and core biopsy were normal. Thoracic and abdominal radiographs and abdominal ultrasound were unremarkable. Ultrasound of the ventral neck identified an oval hypoechoic mass, ~11 mm in diameter, just caudal to the larynx on the left side of the trachea. Surgical exploration and excision of the mass were performed. Touch imprints of the mass were submitted for cytopathology (Figure 1).

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### Cytologic Interpretation

Touch imprints of the ventral neck mass were highly cellular with minimal background hemodilution. A monomorphic population of cells was observed that appeared as free nuclei in a diffuse background of lightly basophilic cytoplasm, typical of endocrine/neuroendocrine tissue (Figure 1). Low numbers of intact cells with round to oval nuclei also were seen. Occasionally, these cells were arranged in acinar structures. Mild to moderate atypical features included anisocytosis, anisokaryosis, a clumped chromatin pattern, and a low number of cells with distinct nucleoli. Some intact cells contained dark black intracytoplasmic granules. Distinct, eosinophilic, needle-shaped structures were observed in the cytoplasm of a low number of the cells. Small, well-differentiated lymphocytes were scattered throughout the imprints.

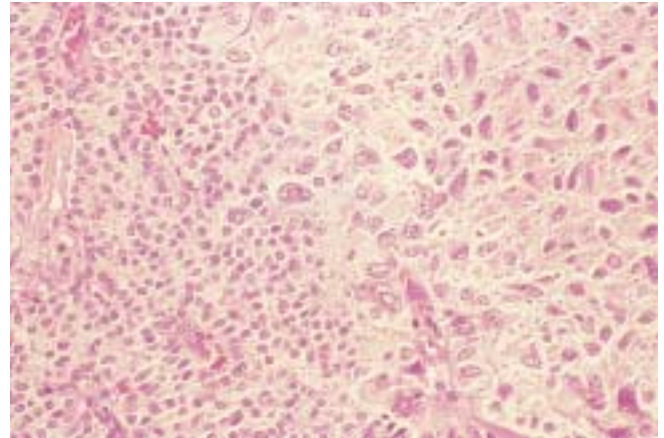
The cytologic interpretation was endocrine/neuroendocrine neoplasia. The cytologic appearance in conjunction with persistent hypercalcemia, signalment, and location of the lesion were consistent with parathyroid neoplasia. The significance of the eosinophilic needle-like structures within the cytoplasm of some cells was unknown.

### Histologic Interpretation

The sample submitted for histologic evaluation contained an infiltrative neoplastic mass that effaced and compressed the surrounding parathyroid gland parenchyma. Neoplastic cells were arranged in sheets, large nests, and irregular cords supported by a fine fibrovascular stroma. Tumor cells were polygonal to slightly elongate, had indistinct cell margins, and contained moderate amounts of pale eosinophilic cytoplasm. Neoplastic cells were generally larger than parathyroid gland epithelial cells, and scattered megalocytic tumor cells were observed (Figure 2). Tumor cell nuclei were central, round to oval, and had finely stippled chromatin. Zero to 2 mitotic figures per  $\times 40$  field were observed within the neoplastic cell population. Based on the clinical history, primary location, cell morphology, irregular infiltrative nature, and the megalocytic cells, a diagnosis of parathyroid gland adenocarcinoma was made.

### Discussion

In the dog, differential diagnoses for hypercalcemia include hypercalcemia of malignancy, hypoadrenocorticism, chronic renal failure, hypervitaminosis D, and primary hyperparathyroidism. Malignancy is the most common of hypercalcemia. Up to 20% of dogs with lym-



**Figure 2.** Histologic section of the ventral neck mass. The neoplastic cells (on the right) are pleomorphic and have larger, more oval-shaped nuclei than the parathyroid gland parenchymal cells (on the left). The diagnosis was parathyroid adenocarcinoma. Hematoxylin and eosin,  $\times 200$ .

phoma and 80-90% of dogs with apocrine gland carcinoma of the anal sac have paraneoplastic hypercalcemia.<sup>1</sup> Other tumors associated with hypercalcemia include multiple myeloma, squamous cell carcinoma, thyroid carcinoma, parathyroid neoplasia, malignant mammary tumors, and thymoma.<sup>1</sup>

A thorough search for neoplasia was pursued in this dog and the only abnormality noted was a small oval hypoechoic mass in the ventral neck. Primary differential diagnoses for ventral cervical masses in the dog include thyroid neoplasia; parathyroid neoplasia; submandibular, medial retropharyngeal, or cervical lymphadenopathy; cellulitis, abscess, or granuloma; sialoadenitis or salivary gland tumors; and less frequently, neoplastic masses such as rhabdomyosarcoma, leiomyosarcoma, or carotid body tumors.<sup>2</sup> Touch imprints of the mass submitted intraoperatively for cytopathology identified it as neuroendocrine in origin. Considering the location, gross appearance, cytologic appearance, and the associated hypercalcemia, a tumor of parathyroid origin was strongly suspected. Results of PTH (normal) and PTHrP (undetectable) tests at the time the dog had persistent hypercalcemia supported a diagnosis of primary hyperparathyroidism. Serum phosphorus level was within the reference range. The calcium concentration dropped below the reference range immediately after surgical excision of the mass and later returned to normal. Histopathology confirmed the diagnosis of parathyroid adenocarcinoma.

Interpretation of the malignant potential of neuroendocrine tumors based on cytologic appearance is difficult.<sup>3</sup> Nuclei from these tumors often do not display sufficient criteria of malignancy, even when the potential for metastasis or invasion is likely.<sup>3</sup> The diagnosis of

benign versus malignant parathyroid neoplasms is based on a combination of gross appearance, histologic features, and, ultimately, biologic behavior of the lesion. Earlier reports indicate that parathyroid adenocarcinomas account for 5% of all neoplastic parathyroid glands.<sup>2</sup> In one study, 2 of 72 dogs (3%) with primary hyperparathyroidism had carcinoma diagnosed histologically.<sup>1</sup> Rare reports exist in the literature of hypercalcemia due to functional parathyroid adenoma in the horse.<sup>4</sup>

Capsular and vascular invasion is a characteristic histologic finding of parathyroid carcinoma.<sup>5</sup> Controlled studies of histologic interpretations by pathologists have indicated that it is difficult, if not impossible, to consistently distinguish between benign and malignant parathyroid tissue. In some cases, benign-appearing cells from parathyroid tumors have histologic evidence of local invasion or metastasis suggestive of a carcinoma.<sup>5</sup> In this dog, the diagnosis of adenocarcinoma was based on infiltration of normal parathyroid gland tissue, and on the presence of megalocytic neoplastic cells. Immunohistochemistry using monoclonal antiparathyroid antibodies has been used for distinguishing between normal and abnormal parathyroid tissue.<sup>5</sup> Determination of DNA ploidy also may be used to establish the nuclear DNA content in an attempt to distinguish between benign and malignant parathyroid tumors.<sup>5</sup> Also, immunohistochemical staining of chromogranin-

A, a secretory granule of endocrine cells, can be used to confirm the presence of secretory granules in endocrine tumor cells.<sup>6</sup>

In summary, parathyroid neoplasia always should be included in the list of differential diagnoses for animals with a ventral neck mass and associated hypercalcemia. The lesion in this dog had cytologic features characteristic of a neuroendocrine tumor. In addition, previously unidentified crystalline-like material was noted in some cells. These needle-like structures were not seen on histologic sections, likely resulting from differences in fixation or stain preparation. Although the origin of this material is unknown, a secretory product of parathyroid origin, likely PTH, is hypothesized. To the authors' knowledge, this is the first report describing in detail the cytologic findings of a parathyroid adenocarcinoma. Therefore, the frequency and origin of the eosinophilic, crystalline-like structures is yet to be determined. ◇

**Key Words:** Adenocarcinoma, canine, cytology, hypercalcemia, parathyroid gland

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