Paraneoplastic hypercalcemia in a canine patient with a mandibular salivary carcinoma

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OBJECTIVE
To describe a novel presentation of paraneoplastic hypercalcemia caused by a canine salivary carcinoma.

ANIMAL
A 6-year-old intact male Husky with hypercalcemia and a spontaneous salivary carcinoma, stage III.

CLINICAL PRESENTATION, PROGRESSION, AND PROCEDURES
The dog presented with polyuria, polydipsia, and hypercalcemia. Physical examination revealed a 37 X 43-mm firm mass in the ventrolateral aspect of the right-hand side of the neck, caudal to the temporomandibular joint. Incisional biopsy was suspicious of metastatic carcinoma to the mandibular lymph node. A full-body CT scan found a large, heterogenous, contrast-enhancing mass on the right ventrolateral neck that appeared to be originating from either the mandibular lymph node or right mandibular salivary gland. Parathyroid hormone–related protein was considered within normal reference intervals, and both parathyroid glands appeared ultrasonographically normal.

TREATMENT AND OUTCOME
The patient was treated with a marginal surgical excision of the mass, without immediate complications. Histopathology confirmed the presence of a salivary carcinoma with narrow margins of excision and invasion of the mandibular lymph node. Twenty-four hours after surgery, ionized calcium returned to normal reference values and clinical signs completely resolved.

CLINICAL RELEVANCE
Hypercalcemia is an urgent pathology with important systemic implications requiring prompt diagnosis and intervention. In this case report, we identify the first salivary carcinoma associated with a paraneoplastic hypercalcemia, including this pathology as a new differential diagnosis. The hypercalcemia resolved with marginal surgical excision, but interestingly the parathyroid hormone–related protein was not overexpressed, meaning that this neoplasia could mediate hypercalcemia by another pathophysiological mechanism.

Keywords: salivary carcinoma, hypercalcemia, mandibular salivary gland, paraneoplastic syndrome, hypercalcemia of malignancy

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nodes were normal in size and shape. Rectal examination did not reveal any abnormalities in either anal gland. The rest of the physical examination was unremarkable.

Diagnostic Findings and Interpretation

Hematology at presentation was unremarkable, and biochemistry confirmed the preexisting hypercalcemia with an elevated ionized calcium (1.78 mmol/L; reference interval, 1.25 to 1.5 mmol/L; Figure 1). Blood parathyroid hormone (PTH) was under the detection limit (< 2.0 mmol/L), and the PTH-related protein (PTHrP) was not elevated (0.4 pmol/L; reference interval, 0 to 0.5 pmol/L). A mild elevation of the AST was noted (48 U/L; reference interval, 0 to 40 U/L) without any apparent clinical significance.

A CT scan of the neck revealed a 31.1 X 44.1-mm irregularly enhancing mass, centered ventrolateral to the right mandibular salivary gland with multiple ill-defined nodular areas showing a mixed soft tissue and fluid attenuation (Figure 2). There was a poor delineation between the mass and rostral aspect of the right salivary gland. The right mandibular lymph nodes were not identifiable, but the remaining lymph nodes were unremarkable. The mass was suspected to arise either within the mandibular lymph node or from the rostral margin of the right mandibular gland. No abnormalities of the thyroid glands were detected on CT scan, but due to the low sensitivity for detection of parathyroid lesions, both glands were also evaluated by ultrasound and no abnormalities were detected. A CT scan of the thorax did not reveal any evidence of metastatic disease, and CT of the abdomen revealed an incidental prostatomegaly with features characteristic of benign prostatic hyperplasia. The mass lesion was suspected to be neoplastic with anaplastic carcinoma or salivary carcinoma, with paraneoplastic hypercalcemia, considered most likely.

Treatment and Outcome

After staging, the patient was started on furosemide (1 mg/kg, PO, q 24 h for 14 days) as palliative treatment to aid calciuresis. No further calcium monitoring was performed until the day after surgical removal, but clinical signs of polyuria and polydipsia persisted.

Thirty-seven days after the detection of hypercalcemia, an exploratory surgery of the right mandibular area was performed via a ventral paramedian approach. Following incision of the skin (including (red arrows) is evident in the ventral aspect of the right neck, displacing the right mandibular gland dorsally. B—Dorsal image showing poor delineation between the cranial aspect of the right mandibular gland (blue arrows) and the caudal aspect of the mass (red arrows), suggesting that the origin of the mass could be the right salivary gland (CT settings were window length, 73 HU; window width, 419 HU; and 1-mm slice thickness).
the biopsy site) and platysma muscle, the mandibular salivary gland and sublingual gland/duct complex were bluntly dissected free of their attachments and excised (Figure 3). The lesion was removed entirely with the right mandibular salivary gland, but no mandibular lymph nodes were visualized or palpated grossly during surgery. To assess early metastatic disease, the right retropharyngeal lymph node was removed for histopathology. Both tonsils were visually checked and appeared normal. Due to the suspected benign prostatic hyperplasia, a routine orchiectomy was performed and no testicular abnormalities were observed macroscopically. Furosemide was discontinued, and ionized calcium levels performed 24 hours following surgical excision of the mass were within reference (1.38 mmol/L; Figure 1).

Histopathology of the mass revealed the presence of normal salivary gland lobules and a highly cellular, infiltrative, malignant epithelial neoplasm composed of large cuboidal cells arranged in acini and lobules supported by moderate fibrous stroma. The epithelial cells had abundant eosinophilic cytoplasm with indistinct cell edges and a round to oval open-faced nucleus with 1 to 3 variably visible nucleoli (Figure 4). Surgical margins were clear but narrow, with < 1 mm. The mitotic count was 5 per 10 hpf (2.37 mm²). There was infiltration by a high number of inflammatory cells, including neutrophils, plasma cells, and lymphocytes. Interestingly, the right mandibular lymph node was identified at the edge of the mass with a focal invasion from the neoplastic lesion. No neoplastic cells were identified in the right retropharyngeal lymph node. The final diagnosis was a stage III (T3N1M0) salivary carcinoma with neutrophilic inflammation.

The patient was reassessed 12 days following surgery, and ionized calcium levels remained within reference range (Figure 1). The previous clinical signs of polyuria and polydipsia had completely resolved, and on clinical examination there was no evidence of local tumor recurrence noted. The patient received adjuvant chemotherapy, with single-agent carboplatin (300 mg/m²) every 3 weeks for 6 doses. Computed tomography scan of the head, thorax, and abdomen performed on day 159 after surgery did not reveal any signs of metastasis or local recurrence. No recurrence of the hypercalcemia, clinical signs, or mass was noted during the follow-up period (183 days).

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**Figure 3**—Intraoperative photographs of the mandibular mass of the patient after a ventral paramedian approach. The patient described in Figure 1 was positioned in dorsal recumbency with the neck extended; the rostral aspect of the head is located downward in the figure. The mass (red arrow) appeared to be adhered to the right mandibular salivary gland (blue arrow) and was dissected with the sublingual duct/gland complex (green arrow).

**Figure 4**—Photomicrographs of the mandibular mass. A—Photomicrograph of the mandibular lymph node of the patient described in Figure 1 infiltrated by cuboidal neoplastic cells arranged in acini and lobules. H&E stain; bar = 500 μm. B—Photomicrograph of the mandibular salivary gland effaced by cuboidal neoplastic cells arranged in acini and lobules with neutrophilic inflammation. One mitotic figure is seen in the image and marked with a red arrow. H&E stain; bar = 50 μm.
Salivary gland pathologies are relatively uncommon in dogs, but the recent literature suggests that neoplasia is a common finding (20.1%) in enlarged glands. In canine patients, the majority of these tumors are considered malignant, with adenocarcinoma being the most common subtype. Other neoplasia such as fibrosarcoma, lymphoma, and mast cell tumor should also be considered. The scarcity of large studies on salivary gland carcinomas makes the biological behavior of these tumors difficult to assess. Salivary carcinomas are locally aggressive, and surgical excision has been generally accepted as the standard of care, achieving long-term control of the disease with median survival times of 498 to 550 days.

Salivary carcinomas are often identified due to the presence of a cervical mass; however, halitosis and dysphagia are also common clinical signs. Interestingly, our patient not only presented with a notable mass but with clinical signs of polyuria and polydipsia, consistent with the subsequent finding of hypercalcemia. Paraneoplastic syndromes are systemic clinical manifestations due to an underlying neoplasia. Paraneoplastic hypercalcemia is the most common cause of hypercalcemia in the dog. Although hypercalcemia has been associated with multiple neoplasms (eg, lymphoma, anal sac adenocarcinoma, mammary, pulmonary, adrenal, hepatocellular, and transitional cell carcinoma), to the authors’ knowledge this was the first report of paraneoplastic hypercalcemia associated with a salivary carcinoma.

Interestingly, the PTHrP was not elevated in this case, which could mean salivary carcinomas mediate hypercalcemia through other pathways. Since this was the first time paraneoplastic hypercalcemia has been associated with a salivary carcinoma, it is not included as a differential diagnosis for hypercalcemia, this report suggests that salivary carcinoma could be considered as a differential in future cases. In this case, marginal surgical excision was able to improve the quality of life and clinical signs of the patient.

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