Serum parathyroid hormone-related protein concentration in a dog with a thymoma and persistent hypercalcemia

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Abstract — A thymoma was tentatively diagnosed by radiographic and cytologic examination in a dog with hypercalcemia and elevated serum parathyroid hormone-related protein (PTHrP) concentration. Following surgical excision, the diagnosis of thymoma was confirmed via histopathologic examination, the hypercalcemia resolved, and the PTHrP concentration decreased to below detectable limits.

Résumé — Concentration sérique de la pseudo-parathormone chez un chien présentant un thymome et une hypercalcémie persistante. Un diagnostic provisoire de thymome a été établi à la suite d'examens radiologique et cytologique chez un chien présentant une hypercalcémie et une concentration sérique élevée de pseudo-parathormone (PTH-rp). Suite à l'excision chirurgicale, le diagnostic de thymome a été confirmé par l'examen histopathologique, l'hypercalcémie a disparue et la concentration de PTH-rp a diminuée en deçà des limites de détection.

(Traduit par docteur André Blouin)

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A 9-year-old, female, Labrador retriever was referred to the teaching hospital at the Atlantic Veterinary College with a history of polyuria, polydipsia, exercise intolerance, weight loss of 5 mo duration, and dyspnea of 6 wk duration. Hypercalcemia was documented 3.5 mo and 3.0 mo previously (3.71 and 3.78 mmol/L, respectively; reference range, 2.24 to 3.04 mmol/L). On examination, the dog was thin, mildly dyspneic, and tachypneic with a respiratory rate of 60 breaths/min. Lung sounds were absent over the cranioventral thorax, bilaterally. Heart sounds were barely audible on the left side of the thorax, and were muffled on the right side.

Thoracic radiographs revealed a large elliptical mass in the cranial mediastinum displacing the cardiac silhouette caudally and laterally to the right. Moderate pleural effusion was present. Thoracic ultrasonography characterized the mass as diffusely hypoechoic with interspersed hyperechoic foci. A complete blood cell count, serum biochemistry profile, and urinalysis were performed. The hemogram was unremarkable. Serum biochemical abnormalities included a marked hypercalcemia (4.35 mmol/L; reference range, 2.24 to 3.04 mmol/L), a mild hypophosphatemia (0.79 mmol/L, reference range, 0.82 to 1.87 mmol/L), a mild hyperglycemia (7.0 mmol/L; reference range, 3.3 to 5.6 mmol/L), and a mild increase in serum alanine aminotransferase (ALT) activity (108 U/L, reference range: 5 to 69 U/L). As a mediastinal mass was present, the hypercalcemia and hypophosphatemia were attributed to a possible paraneoplastic syndrome, although, initially, other causes could not be ruled out. The mild hyperglycemia was considered to be due to stress, and the mild increase in ALT indicated mild hepatocellular leakage. Urinalysis performed on a urine sample collected via cystocentesis revealed a urine specific gravity of 1.015, without concurrent azotemia or clinical dehydration, bacteriuria, and pyuria. Hemolytic *Escherichia coli* were obtained on urine culture.

Cytologic evaluation was performed on a single, transthoracic fine needle aspirate of the mediastinal mass. The sample contained large numbers of nucleated cells. The majority of cells (90%) were small lymphocytes; lower numbers of medium to large lymphocytes (8%), mast cells (1%), nondegenerate neutrophils (1%), and rare eosinophils (< 1%) were also seen. Thymoma was the primary differential diagnosis, based on the cytologic, radiographic, ultrasonographic, and physical examination findings.

Sodium chloride solution (0.9% Sodium Chloride Injection USP; Baxter, Toronto, Ontario) was administered, IV, at a dosage of 125 mL/kg body weight (BW)/d to reduce the calcium concentration by dilution, increase renal perfusion, and induce a sodium-dependent calciuresis. This therapy was instituted because prolonged hypercalcemia can lead to renal failure, arrhythmias, encephalopathy, coma, and death (1). Furosemide (Lasix; Hoechst, Regina, Saskatchewan), 2 mg/kg BW, SC, q8h, was also administered to maintain the calciuresis. After 24 h of symptomatic therapy, the serum calcium concentration had decreased to 3.2 mmol/L. Administration of an oral formulation of furosemide (Apo-Furosemide; Apotex, Weston, Ontario) was initiated, and the dosage of IV fluids was gradually discontinued. Amoxicillin (Amoxil; SmithKline Beecham, Mississauga, Ontario), 10 mg/kg BW, PO, q12h, for 3 wk, was administered to treat the urinary tract infection.

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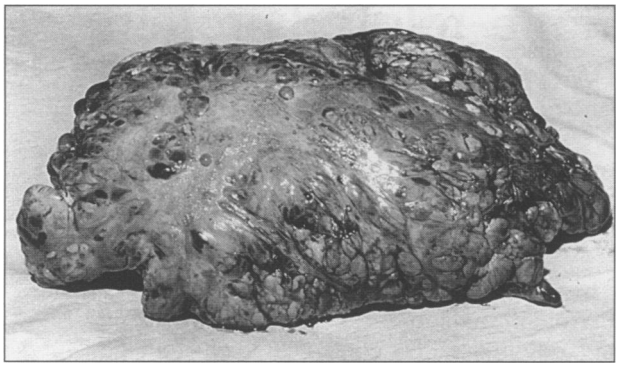

Figure 1. Photograph of the gross appearance of a thymoma removed from a 9-year-old dog. The mass measured approximately 25 cm at its widest dimension.

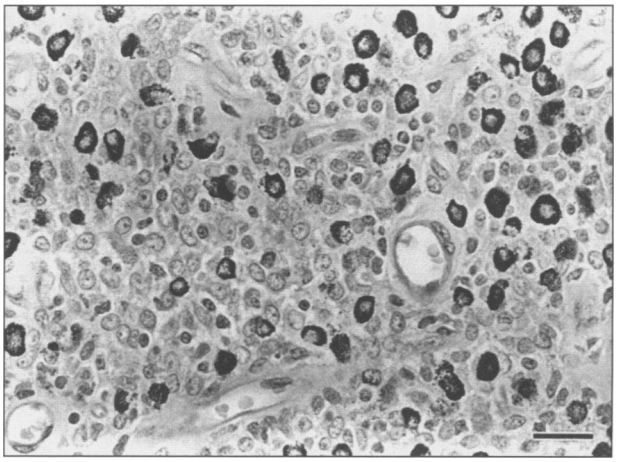

Figure 2. Photomicrograph of a thymoma from a dog showing numerous mast cells (with positively stained cytoplasmic granules) between tumor cells. Toluidine blue stain; bar = 25 μm.

Following 3 d of medical management, the mass was surgically excised. Four milligrams of morphine sulfate (Morphine Sulfate Injection; Abbott Laboratories, St. Laurent, Quebec) was administered epidurally between the 7th lumbar and 1st sacral vertebrae. A ventral midline skin incision and median sternotomy were performed to expose the thoracic cavity. It was necessary to transect the sternum from the manubrium to the xiphoid cartilage and diaphragm in order to visualize and exteriorize the mass. The vessels supplying the mass were ligated and transected, and the mass was carefully dissected free from surrounding tissues and completely excised. The mass measured approximately 25 cm × 10 cm × 15 cm (Figure 1) and appeared well encapsulated and lobulated. Several small tags of material, which could have represented either fibrin or tumor, were palpated within the cranial vena cava. Due to the risk involved in accessing this material, it was not biopsied. A 24-French thoracostomy tube (Argyle Trocar Thoracic Catheter; Sherwood Medical, St. Louis, Missouri, USA) was placed in the left side at the 5th intercostal space. The sternum was closed by using figure-8 orthopedic wires around each sternebra and incorporating the costochondral junctions. The intercostal nerves were blocked by injecting bupivacaine (Marcaine; Sanofi Winthrop, Markham, Ontario) to aid in the control of postoperative pain.

Histologically, the mass consisted of sheets of small lymphocytes interspersed with larger, round- to polygon-shaped epithelial cells. The epithelial cells displayed moderate to marked anisokaryosis, but mitotic figures were not evident. Large numbers of mast cells containing granules, which stained positively with toluidine blue, were also present throughout the mass (Figure 2). The histologic findings were compatible with a non-invasive, encapsulated, mixed lymphoepithelial thymoma.

The dog recovered uneventfully from surgery. Lactated Ringer's solution (Lactated Ringer's Injection USP; Baxter), with 16 mEq/L of added potassium chloride (Potassium Chloride; Astra Pharmaceuticals, Mississauga, Ontario), was administered at a rate of 63 mL/kg BW/d for 2 d. Morphine sulfate, 0.1 mg/kg BW, was administered, q4h, as needed for analgesia during the first 12 h after surgery. Heparin (Heparin Leo; Leo Laboratories, Ajax, Ontario), 5 IU/kg BW, SC, q8h, for 3 d, was administered to prevent possible thromboembolic disease. The amoxicillin was discontinued, and ampicillin (Ampicillin Sodium; Novopharm, Toronto, Ontario) was given at 21 mg/kg BW, IV, q8h, for the 12 h immediately after surgery. Twelve hours postoperatively, the patient developed paroxysmal ventricular tachycardia that was controlled with a constant rate IV infusion of lidocaine (Lurocaine; Austin, Joliette, Quebec) at a dose of 40 g/kg BW/min. The paroxysmal ventricular tachycardia resolved when the chest tube was removed 48 h after surgery. The total serum calcium concentration decreased to 2.2 mmol/L, 2.08 mmol/L, and 1.86 mmol/L at 1, 2, and 3 d following surgery, respectively. At 3 d postoperatively, calcium gluconate (Calcium Gluconate 10% Injection USP; Abbott Laboratories), 28 mg/kg BW, was administered, SC, to avoid complications resulting from hypocalcemia. The following day (4 d after surgery), the total serum calcium concentration had increased to 2.01 mmol/L.

Immunoradiometric assays for serum parathyroid hormone-related protein concentration (PTHrP; INCSTAR, Stillwater, Minnesota, USA) and endogenous parathyroid hormone concentration (PTH; Diagnostic Products, Los Angeles, California, USA) were performed at the Animal Health Diagnostic Laboratory, Michigan State University, East Lansing, for samples collected 3 d prior to and 3 d following surgery. The preoperative serum PTHrP and endogenous PTH concentrations were 15.1 pmol/L (reference range, < 0.2 pmol/L) and 1 pmol/L (reference range, 2–13 pmol/L), respectively. The postoperative serum PTHrP and endogenous PTH concentrations were 0.0 pmol/L and 5 pmol/L, respectively. An acetylcholine receptor antibody concentration (Comparative Neuromuscular Laboratory, San Diego, California, USA), determined preoperatively, was 0.1 nmol/L (reference range, < 0.6 nmol/L). The patient was discharged on the 5th day after surgery with instructions to the owner to continue administration of amoxicillin, at a dosage of 10 mg/kg BW, PO, q12h, and calcium carbonate (West Care Calcium Carbonate; Pharmavite, Mississauga, Ontario), 20 mg/kg BW, PO, q12h.

Thymomas are uncommon tumors found in the cranial mediastinum of dogs (2–5). They consist of neoplastic thymic epithelial cells infiltrated with variable numbers of nonneoplastic mature lymphocytes (1,2,5). This tumor is most frequently diagnosed in middle-aged to older dogs, with mean ages of 8.7 y (2) and 9 y (5) reported. Thymomas have been associated with several paraneoplastic syndromes, including myasthenia gravis (2,5), nonthymic cancer (2,5), polymyositis (2,5), and, infrequently, hypercalcemia (3,4,6,7). Myasthenia gravis (MG) has been reported in 18% to 47% of cases of thymoma (5,8,9). In one study, hypercalcemia was present in 2 of 23 dogs (8.7%) with thymoma (4). The histologic and cytologic appearance of thymomas does not correlate with malignancy (2,5), so thymomas are usually classified as benign or malignant, based on their invasiveness or resectability (5). Prognosis depends on surgical resectability and the presence or absence of megaesophagus. The prognosis for dogs with surgically resectable thymomas in the absence of megaesophagus is good, with 83% of dogs having a 1-year survival time (4). Patients with nonresectable tumors currently have a poor prognosis, but chemotherapy or radiation therapy may offer an improved prognosis in the future (5). Dogs with concurrent megaesophagus have a poor prognosis, with a 16-day mean survival time in one study; the majority of dogs in this study died of megaesophagus-associated aspiration pneumonia (4).

Malignancy-associated hypercalcemia (MAHC) is the most common cause of hypercalcemia in dogs (10,11). Malignancy-associated hypercalcemia is most commonly associated with lymphosarcoma, but can also occur with other neoplasms, such as apocrine cell adenocarcinoma of the anal sac, multiple myeloma, squamous cell carcinoma, thyroid adenocarcinoma, malignant mammary tumors, testicular interstitial cell tumors, and thymomas (3,10,11). Two mechanisms are believed to cause MAHC. The first mechanism is local osteolytic hypercalcemia, which occurs when tumor cells invade bone or bone marrow and produce locally acting bone-resorbing factors (10,12). The second mechanism, known as humoral hypercalcemia of malignancy, occurs when tumor tissue remote from bone produces one or more factors that stimulate osteoclastic bone resorption (10). Parathyroid hormone related protein (PTHrP) is considered the most important of these humoral factors, because it is the most consistent feature of humoral hypercalcemia of malignancy, and it shares most of the biologic activities of parathyroid hormone (PTH) (12).

Hypercalcemia has been reported previously in cases of thymoma in dogs (3,4,6,7). One article on serum PTHrP and PTH concentrations in 58 dogs with cancer-associated hypercalcemia included a dog with a thymoma and an elevated PTHrP concentration, although the specific PTHrP concentration was not reported (13). The present case, therefore, is believed to be the first full case report of a canine thymoma in which an increased PTHrP concentration has been documented. The rapid decline in the PTHrP concentration following surgical removal of the mass, coupled with resolution of the hypercalcemia, support a neoplastic origin of the hypercalcemia. The decreased serum endogenous PTH concentration prior to surgery suggests normally functioning parathyroid glands producing less PTH in the face of hypercalcemia. The rapid normalization of serum endogenous PTH concentration 3 d after surgery likewise suggests that the return to normal PTH production followed resolution of the hypercalcemia.

Polyuria and polydipsia resolved in this dog following surgery. It is likely that hypercalcemia was the cause of these clinical signs. Hypercalcemia directly impairs the ability of renal tubules to respond to antidiuretic hormone (14). This results in decreased resorption of water and clinical signs of polyuria and polydipsia.

Although thymomas are uncommon, this tumor type should always be considered among the differential diagnoses for cranial mediastinal masses in dogs. Potential exists for confusion with lymphosarcoma, which is more common at this site and is often associated with hypercalcemia (3,5,12). Other differential diagnoses for cranial mediastinal masses include metastatic neoplasia, chemodectoma, branchial cyst, ectopic thyroid or parathyroid tissue, and abscess or granuloma. Transthoracic aspiration of the mass from the dog in this report revealed lymphoid cells with no epithelial component. A mixed population of epithelial cells and small lymphocytes is frequently observed in aspirates from thymomas; often lymphocytes dominate and epithelial cells may be absent (2,4,5). The preponderance of small lymphocytes, however, as opposed to the large, often blastic, lymphoid cells seen in the majority of cases of lymphosarcoma should guide cytologists away from a diagnosis of lymphosarcoma. The presence of mast cells in the aspirate in this case also supported a diagnosis of thymoma (4). In one study, mast cells were seen in 53% of fine needle aspirates and 85% of thymomas stained with toluidine blue (4). The ultrasonographic appearance of the mass was also not supportive of lymphosarcoma, which typically has a homogeneous hypoechoic appearance (15). Distinguishing between thymoma and lymphosarcoma is critical, as the treatment is radically different. Surgical resection is the treatment of choice for thymomas; chemotherapy is utilized in the treatment of lymphosarcoma (4,5).

Myasthenia gravis can be associated with thymomas in dogs (2,5), and MG-associated megaesophagus, if present, greatly worsens the prognosis (4). Measuring the serum acetylcholine receptor antibody concentration in dogs with thymoma will determine if MG is present or not. In the dog in this report, the acetylcholine receptor antibody concentration was within normal limits.

The total serum calcium concentrations at 10 and 45 d postsurgery were 2.48 mmol/L and 2.51 mmol/L, respectively. Oral calcium supplementation was discontinued 10 d postoperatively. Five months postoperatively, however, this dog presented with a history of weakness and inappetence for several days. Thoracic radiographs were within normal limits. The total serum calcium concentration was 4.85 mmol/L, and azotemia was present (urea 16.4 mmol/L, reference range 3.0–10.5 mmol/L; creatinine 166 mol/L, reference range 60–140 mol/L). A concurrent urine sample was not available. The dog was euthanized. A postmortem examination was not performed.

Acknowledgments

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BOOK REVIEW

COMPTE RENDU DE LIVRE

Kennedy MJ, MacKinnon JD, Higgs GW. ***Veterinary Parasitology — Laboratory Procedures.*** Alberta Agriculture, Food and Rural Development, Edmonton, Alberta, ISBN 0-7732-6136-2, 1998 CDN$32.00 + GST.

This spiral-bound laboratory manual is a compilation of diagnostic and research techniques used in the recovery and identification of various stages of helminth, protozoan, and arthropod parasites of veterinary interest. The manual describes the details of the procedures and provides pertinent discussion of the techniques, giving the reader a basis to understand when and where the techniques should be applied.

The text is concise and easy to read. There has long been a need for an updated text devoted to this area, and the authors should be commended for their handling of this subject. I had a minor difference of opinion with just a few of the recommendations made by the authors; however, I have found this book to be very useful and would strongly recommend it for purchase by any veterinary diagnostic or research laboratory. Veterinarians in private practice should also consider purchasing this book, due to its wealth of easily accessible information on basic parasitology diagnostics and its moderate price.

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