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Topical Review

Paraneoplastic Hypercalcemia

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A B S T R A C T

Paraneoplastic syndromes (PNSs) are neoplasm-associated alterations in bodily structure or function or both that occur distant to the tumor. They are an extremely diverse group of clinical aberrations that are associated with the noninvasive actions of the tumor. In many situations, the PNS parallels the underlying malignancy, and therefore, successful treatment of the tumor leads to disappearance of the PNS. Alternatively, recurrence of the PNS after successful treatment signals recurrence of the tumor, and the return of the PNS often significantly precedes the detectable recurrence of the tumor. This is often the case with paraneoplastic hypercalcemia, often referred to as hypercalcemia of malignancy (HM). The most common cause of hypercalcemia in dogs is cancer. Neoplasia is diagnosed in approximately two-thirds of dogs with hypercalcemia vs. approximately one-third in cats. A variety of tumors have been associated with HM. Lymphoma is the most common cause of HM, and the most common anatomical site for dogs with lymphoma-associated HM is the cranial mediastinum. Other tumors associated with HM in dogs and cats include anal sac apocrine gland adenocarcinoma, thyroid carcinoma, multiple myeloma, bone tumors, thymoma, squamous cell carcinoma, mammary gland carcinoma/adenocarcinoma, melanoma, primary lung tumors, chronic lymphocytic leukemia, renal angiomyxoma, and parathyroid gland tumors. As HM is a potential medical emergency, the primary goal in cases of HM is the elucidation of the underlying cause and thereby instituting the appropriate specific therapy.

Paraneoplastic syndromes (PNSs) are neoplasm-associated alterations in bodily structure or function or both that occur distant to the tumor. They are an extremely diverse group of clinical aberrations that are associated with the noninvasive actions of the tumor. In many situations, the PNS parallels the underlying malignancy, and therefore, successful treatment of the tumor leads to disappearance of the PNS. Alternatively, recurrence of the PNS after successful treatment signals recurrence of the tumor, and the return of the PNS often significantly precedes the detectable recurrence of the tumor. This is often the case with paraneoplastic hypercalcemia, often referred to as hypercalcemia of malignancy (HM).

The most common cause of hypercalcemia in dogs is cancer. A variety of tumors have been associated with HM. Neoplasia is diagnosed in approximately two-thirds of dogs with hypercalcemia[1,2] vs. approximately one-third in cats.[3] Lymphoma (LSA) is the most common cause of HM, and the most common anatomical site for dogs with LSA-associated HM is the cranial mediastinum. Other tumors associated with HM in dogs and cats include anal sac apocrine gland adenocarcinoma, thyroid carcinoma, multiple myeloma, bone tumors, thymoma, squamous cell carcinoma, mammary gland carcinoma/adenocarcinoma, melanoma, primary lung tumors, chronic lymphocytic leukemia, renal angiomyxoma, and parathyroid gland tumors.[4-12] Unfortunately, the incidence of HM in veterinary oncology patients is unknown; however, HM is seen in 10%-35% of dogs with LSA, $\geq$25% of dogs with anal sac apocrine gland adenocarcinoma, and approximately 20% of dogs with myeloma.[13,14] In addition, HM is seen in 5%-30% of human cancer patients.[15,16]

The causes of HM are varied and include ectopic production of parathormone (PTH) or PTH-related peptide (PTH-rp) by the tumor, extensive lytic bone metastases, primary hyperparathyroidism, tumor-associated prostaglandins ($PGE_{1/2}$), interleukin-1beta (previously known as osteoclast-activating factor), transforming growth factor-beta, and receptor activator of nuclear factor kappa beta ligand.[8,15,17-22] Interestingly, transforming growth factor-beta1 regulates the messenger ribonucleic acid stability of PTH-rp.[23] The HM seen in LSA and anal sac apocrine gland adenocarcinoma is commonly caused by tumor-associated PTH-rp.[24,25] PTH-rp is a 16-kDa protein with significant sequence identity to PTH, suggesting that the hypercalcemia seen in PTH-rp-associated HM is due to the ability of PTH-rp to act and function like PTH. In addition to HM, other hypercalcemia differentials, such as laboratory error (lipemia and hemolysis), acute renal failure, hypervitaminosis D, hypoadrenocorticism, granulomatous disease, and others, may be considered.

In addition to ensuring that the hypercalcemia is not due to lipemia or hemolysis, it is potentially important to interpret the calcium value in relation to the level of serum albumin. Two commonly utilized correction formulas that controversially attempt to account for the level of serum albumin are as follows:

$$\text{Adjusted calcium (mg/dL)} = [\text{Calcium (mg/dL)} - \text{albumin (g/dL)}] + 3.5$$

OR

$$\text{Adjusted calcium (mg/dL)} = \text{Calcium (mg/dL)} - [\text{total serum protein (g/dL)} \times 0.4] + 3.3$$

Similarly, an increase in the free ionized fraction of calcium can occur with acidosis. Acidotic HM patients may have an increase in clinical signs of hypercalcemia when compared to nonacidotic HM patients.

The primary clinical manifestations of HM are due to renal function impairment. Severe HM (calcium $>$ 18 mg/dL) should be considered a *medical emergency*. An inability to concentrate urine is noted first due to decreased responsiveness to antidiuretic hormone at the distal tubule; the calcium then decreases renal blood flow and glomerular filtration rate due to severe

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Table 1
Treatment for Hypercalcemia of Malignancy

Elimination of the inciting tumor is the primary goal for all categories of hypercalcemia!
Mild hypercalcemia and minimal clinical signs
Rehydration with normosaline (0.9% NaCl)
Moderate hypercalcemia and clinical signs
Rehydration with normosaline (0.9% NaCl)
Continue normosaline diuresis (urine output >2 mL/kg/h)
Furosemide (1-4 mg/kg every 8-24 h IV or PO)
Note: Use only after patient is fully rehydrated
Prednisone (1 mg/kg daily to BID PO)
Note: Use only after diagnosed (see text)
Severe hypercalcemia and severe clinical signs
Oncologic emergency!!
See moderate hypercalcemia treatments
For refractory cases:
Mithramycin (25 μg/kg IV 1-2 times/wk)
Note: Sclerosing agent and hepatotoxin at higher doses
Biphosphonates
Pamidronate (1-1.5 mg/kg IV q 2-3 wk)
Salmon calcitonin (4-10 MRC units/kg SQ daily)
Gallium nitrate (not evaluated to date in veterinary medicine)

Abbreviations: IV, intravenously; PO, per os; BID, bis in die; MRC, Medical Research Council; SQ, subcutaneously.

vasoconstriction. Calcium salt deposition in the renal parenchyma further compounds the prerenal and renal azotemia. The urinary epithelium may then undergo degeneration and, in severe cases, necrosis. The situation clinically worsens as the patient becomes severely polyuric and polydypsic, begins vomiting, and then undergoes continual and progressive dehydration. In addition to its effects on the renal system, in severe cases of HM, one may see constipation, hypertension, twitching, weakness, shaking, depression, vomiting, bradycardia, stupor, and possibly coma and death.

The diagnosis of HM can be extremely difficult in some cases. Other laboratory findings commonly seen in HM cases include azotemia with hypophosphatemia to normophosphatemia. Extremely advanced HM cases with severe renal destruction may have hyperphosphatemia, even though hyperphosphaturia is a common feature of this PNS. When true HM has been diagnosed, appropriate steps for identification of the cause are immediately necessary. When azotemia is also present in HM cases, this represents a true *medical emergency* for delineation of the cause of the HM and for appropriate therapy. The diagnostic steps for HM should include those undertaken for the staging of LSA in addition to a rectal palpation/examination for anal sac apocrine gland adenocarcinoma. If these diagnostics do not confirm the specific cause of the HM, then the aforementioned hypercalcemia differentials should be considered and appropriately pursued. Dogs and cats with HM would typically have low PTH and high PTH-rp concentrations; however, the cause of the HM can usually be delineated with appropriate diagnostics long before the return of PTH/PTH-rp assay results. Similarly, the astute clinician remembers that there are other causes of HM other than LSA or anal sac apocrine gland adenocarcinoma, and therefore, a thorough physical examination and staging is tantamount to successful delineation of the causes in HM cases.

As HM is a potential medical emergency, the primary goal in cases of HM is the elucidation of the underlying cause and thereby instituting the appropriate specific therapy. Though often necessary when searching for the underlying cause of the HM, symptomatic therapy must be judiciously utilized. The premature administration of symptomatic therapy, such as the use of corticosteroids prior to the confirmation of the cause of the HM, can be a very serious problem. If LSA is the underlying cause of the HM, the use of corticosteroids may interfere with the ability to confirm the diagnosis of LSA, necessitating either additional diagnostics or waiting to determine whether the LSA reappears after glucocorticoid administration is discontinued or both. In addition to the implications of diagnostic interference in LSA, glucocorticoids may induce resistance to other chemotherapy agents with a decrease in the ability to induce a complete remission as well as a decrease in the length of survival.[26] Therefore, the use of corticosteroids in cases of undiagnosed hypercalcemia is strongly discouraged.

Symptomatic therapies that promote external loss of calcium, increase renal excretion of calcium, and inhibit bone reabsorption may be utilized in HM patients. The severity of clinical signs and associated hypercalcemia determine the preferred therapy. The use of 0.9% NaCl intravenously is commonly utilized to ameliorate the aforementioned dehydration with expansion of the extracellular fluid volume. In addition, the use of intravenous 0.9% NaCl would increase glomerular filtration rate, increase calciuresis and natriuresis, and decrease calcium reabsorption by the kidneys. Once fully rehydrated, the loop diuretic furosemide with continued normosaline diuresis can be utilized to potently inhibit calcium reabsorption in the ascending loop of Henle. In addition, if the specific cause of the HM is delineated, corticosteroids can be extremely effective in the adjunct treatment of HM by its inhibition ofprostaglandin E, osteoclast-activating factor, vitamin D, and intestinal calcium absorption. Corticosteroids can also be cytotoxic to LSA cells, which as discussed earlier is the most common cause of HM. The most common therapies utilized in the treatment of HM are outlined in Table 1. In rare cases that are unresponsive to the above-mentioned symptomatic therapies and treatment of the underlying cause, other treatments, such as calcitonin, bisphosphonates, or gallium nitrate, may be utilized.[27] Bisphosphonates have become the standard of therapy for human nonhumoral HM due to their potent inhibition of bone resorption without affecting tubular calcium reabsorption.[28] The use of bisphosphonates in dogs and cats appears to be a promising new treatment for hypercalcemia but requires additional study.[29,30] In the future, likely treatment options for HM may include osteoprotegerins, more potent bisphosphonates, anti-PTH-rp antibodies, noncalcemic calcitriol analogs, distal tubule calcium reabsorption inhibitors, receptor activator of nuclear factor kappa beta ligand antagonists, and new bone resorption inhibitors.[28,31]

References

1. Uehlinger P, Glaus T, Hauser B, Reusch C. Differential diagnosis of hypercalcemia—a retrospective study of 46 dogs. *Schweiz Arch Tierheilkd* **140:**188–197, 1998
2. Elliott J. Hypercalcemia in the dog: a study of 40 cases. *J Small Anim Pract* **32:**564–567, 1991
3. Savary KC, Price GS, Vaden SL. Hypercalcemia in cats: a retrospective study of 71 cases (1991-1997). *J Vet Intern Med* **14:**184–189, 2000
4. Sheafor SE, Gamblin RM, Couto CG. Hypercalcemia in two cats with multiple myeloma. *J Am Anim Hosp Assoc* **32:**503–508, 1996
5. Pressler BM, Rotstein DS, Law JM, et al. Hypercalcemia and high parathyroid hormone-related protein concentration associated with malignant melanoma in a dog. *J Am Vet Med Assoc* **221:**263–265, 240, 2002
6. Kleiter M, Hirt R, Kirtz G, Day MJ. Hypercalcaemia associated with chronic lymphocytic leukaemia in a Giant Schnauzer. *Aust Vet J* **79:**335–338, 2001
7. Anderson TE, Legendre AM, McEntee MM. Probable hypercalcemia of malignancy in a cat with bronchogenic adenocarcinoma. *J Am Anim Hosp Assoc* **36:**52–55, 2000
8. Weller RE, Hoffman WE. Renal function in dogs with lymphosarcoma and associated hypercalcemia. *J Small Anim Pract* **33:**61–66, 1992
9. Klausner JS, Bell FW, Hayden DW, et al. Hypercalcemia in two cats with squamous cell carcinoma. *J Am Vet Med Assoc* **196:**103–105, 1990
10. Elliott J, Dobson JM, Dunn JK, et al. Hypercalcemia in the dog: a study of 40 cases. *J Small Anim Pract* **32:**564–571, 1991

11. Messinger JS, Windham WR, Ward CR. Ionized hypercalcemia in dogs: a retrospective study of 109 cases (1998-2003). *J Vet Intern Med* **23:**514–519, 2009
12. Gajanayake I, Priestnall SL, Benigni L, English K, Summers BA, Garden OA. Paraneoplastic hypercalcemia in a dog with benign renal angiomyxoma. *J Vet Diagn Invest* **22:**775–780, 2010
13. Ross JT, Scavelli TD, Matthieson DT, Patnaik AK. Adenocarcinoma of the apocrine glands of the anal sac in dogs: a review of 32 cases. *J Am Anim Hosp Assoc* **27:**349–355, 1991
14. Meuten DJ, Cooper BJ, Capen CC, et al. Hypercalcemia associated with an adenocarcinoma derived from the apocrine glands of the anal sac. *Vet Pathol* **18:**454–471, 1981
15. John WJ, Patchell RA, Foon KA. Paraneoplastic Syndromes. In: DeVita VT, Hellman S, Rosenberg SA, editors. *Cancer: Principles and Practice of Oncology.* ed 5. Philadelphia: Lippincott-Raven Publishers; 1997. p. 2397–2422
16. Pelosof LC, Gerber DE. Paraneoplastic syndromes: an approach to diagnosis and treatment. *Mayo Clin Proc* **85:**838–854, 2010
17. Hofbauer LC, Neubauer A, Heufelder AE. Receptor activator of nuclear factor-kappaB ligand and osteoprotegerin: potential implications for the pathogenesis and treatment of malignant bone diseases. *Cancer* **92:**460–470, 2001
18. Rosol TJ, Nagode LA, Couto CG, et al. Parathyroid hormone (PTH)-related protein, PTH, and 1,25-dihydroxyvitamin D in dogs with cancer-associated hypercalcemia. *Endocrinology* **131:**1157–1164, 1992
19. Forrester SD, Fallin EA. Diagnosing and managing the hypercalcemia of malignancy. *Vet Med* **1:**39, 1992
20. Cryer PE, Kissane JM. Clinicopathologic conference: malignant hypercalcemia. *Am J Med* **65:**486–494, 1979
21. Weir EC, Norrdin RW, Matus RE, et al. Humoral hypercalcemia of malignancy in canine lymphosarcoma. *Endocrinology* **122:**602–608, 1988
22. Barger AM, Fan TM, de Lorimier LP, Sprandel IT, O'Dell-Anderson K. Expression of receptor activator of nuclear factor kappa-B ligand (RANKL) in neoplasms of dogs and cats. *J Vet Intern Med* **21:**133–140, 2007
23. Sellers RS, Capen CC, Rosol TJ. Messenger RNA stability of parathyroid hormone-related protein regulated by transforming growth factor-beta1. *Mol Cell Endocrinol* **188:**37–46, 2002
24. Bolliger AP, Graham PA, Richard V, Rosol TJ, Nachreiner RF, Refsal KR. Detection of parathyroid hormone-related protein in cats with humoral hypercalcemia of malignancy. *Vet Clin Pathol* **31:**3–8, 2002
25. Weir EC, Burtis WJ, Morris CA, Brady TG, Insogna KL. Isolation of 16,000-dalton parathyroid hormone-like proteins from two animal tumors causing humoral hypercalcemia of malignancy. *Endocrinology* **123:**2744–2751, 1988
26. Price GS, Page RL, Fischer B, et al. Efficacy and toxicity of doxorubicin/cyclophosphamide maintenance therapy in dogs with multicentric lymphosarcoma. *J Vet Intern Med* **5:**259–262, 1991
27. Nelson KA, Walsh D, Abdullah O, et al. Common complications of advanced cancer. *Semin Oncol* **27:**34–44, 2000
28. Hurtado J, Esbrit P. Treatment of malignant hypercalcaemia. *Expert Opin Pharmacother* **3:**521–527, 2002
29. Milner RJ, Farese J, Henry CJ, Selting K, Fan TM, de Lorimier LP. Bisphosphonates and cancer. *J Vet Intern Med* **18:**597–604, 2004
30. Hostutler RA, Chew DJ, Jaeger JQ, Klein S, Henderson D, DiBartola SP. Uses and effectiveness of pamidronate disodium for treatment of dogs and cats with hypercalcemia. *J Vet Intern Med* **19:**29–33, 2005
31. Sato K, Onuma E, Yocum RC, et al. Treatment of malignancy-associated hypercalcemia and cachexia with humanized anti-parathyroid hormone-related protein antibody. *Semin Oncol* **30**(5 Suppl 16):167–173, 2003