

Paraneoplastic Syndromes in Dogs and Cats

Paraneoplastic syndromes (PNSs) result in changes to bodily structure or function that are not directly related to the primary tumor or metastasis. These are most commonly caused by tumor production of small molecules such as hormones or cytokines. Sometimes the first sign of cancer in a patient is the PNS, therefore it is important to be able to recognize them and to know what cancers to have on a differential list. If the cancer is treated successfully, then the PNS should resolve; patients need to be monitored for that PNS as that may be the first sign of early recurrence of cancer. Many PNSs have been characterized in the dog and cat; only the more common ones will be outlined here.

Hypercalcemia of Malignancy

The most likely differential for hypercalcemia in dogs is hypercalcemia of malignancy (HM), and a cancer work-up should be done in those patients unless a clear non-neoplastic reason for hypercalcemia has already been identified. The most common tumors that are associated with HM are lymphoma, anal sac apocrine gland adenocarcinoma (AGASACA), multiple myeloma, and thymomas. In T-cell lymphoma, up to 50% of dogs are diagnosed with HM and up to 25% of dogs with AGASACA have HM.

The most common cause of HM is from tumor production of parathyroid hormone-related peptide (PTHrP), though several other cytokines can also cause this (IL-1, IL-6, TNF, etc.). The most common clinical sign associated with hypercalcemia in dogs is polyuria/polydipsia (PU/PD). In a dog presenting with hypercalcemia, a cancer 'hunt' should be performed in the absence of any other clear reason for the elevated calcium. A thorough physical exam should be performed including palpation of all the peripheral lymph nodes as well as rectal exam and emptying of the anal sacs. Thoracic radiographs may reveal a cranial mediastinal mass (consistent with thymoma or lymphoma) or lytic vertebral body lesions (suggestive of multiple myeloma), and abdominal ultrasound may reveal enlarged intra-abdominal lymph nodes or changes to the spleen and liver warranting fine needle aspirate and cytology. Measurement of PTH and calcitriol levels may be needed to rule in/out primary hyperparathyroidism. Lastly, a bone marrow aspirate may need to be performed to rule out aleukemic leukemia. Steroids should never be used for calciuresis until lymphoma/leukemia has been completely ruled out. Removal of the underlying cause (surgery or chemotherapy) is the most effective way to treat HM, and calcium should be monitored closely as it may indicate relapse of the cancer¹.

Hypoglycemia

Overproduction of insulin by an insulinoma is the most common cause of paraneoplastic hypoglycemia in dogs. A diagnosis of insulinoma is made by documenting normal or elevated levels of insulin in the face of hypoglycemia. Other tumor types that have been associated with hypoglycemia are primary liver tumors and leiomyomas/leiomyosarcomas. Patients with a large tumor burden in lymphoblastic leukemia may be hypoglycemic due to excessive consumption of glucose.

Thrombocytopenia

Cancer-associated thrombocytopenia can occur due to decreased production, increased destruction, or consumption. Immune-mediated thrombocytopenia (ITP) is most commonly associated with lymphoma in dogs. In dogs with ITP secondary to their lymphoma, treatment of the lymphoma resolves the thrombocytopenia. Oftentimes, recurrence of thrombocytopenia can be an indicator of relapse of lymphoma prior to being able to clinically appreciate recurrence/progression of the disease. Increased consumption can be resultant of the hypercoagulable state that many cancer patients are in^{2,3}.

Hypertrophic Osteopathy

Hypertrophic osteopathy (HO) is a disorder that causes periosteal proliferation of the long bones. This is usually bilateral and typically starts on the digits and then moves proximally. This is most commonly seen in dogs with primary lung tumors or pulmonary metastasis (especially metastatic osteosarcoma). Patients with HO present with swollen, painful limbs and have difficulties ambulating⁴. Radiographs of the distal limbs will show periosteal proliferation of the long bones, and in those cases thoracic radiographs should be performed next to evaluate for pulmonary disease. The pathogenesis of this process is not well understood. In dogs with primary lung tumors, surgery to remove them can resolve the HO. However, most dogs present with pulmonary metastasis, and metastatectomy is generally not recommended.

Hyperglobulinemia/Hyperviscosity

Hyperglobulinemia is caused by tumor cells overproducing immunoglobulin. This is seen most commonly in dogs with multiple myeloma or cats with myeloma related disorder (MRD). In patients presenting with elevated globulins on blood work, additional work-up is warranted. Thoracic radiographs should be performed and may identify lytic lesions in the vertebral bodies. Serum or urine electrophoresis can be performed to identify a monoclonal gammopathy. Cats often have visceral involvement with MRD, and an abdominal ultrasound with aspirates of the spleen (+ any other abnormal organs on ultrasound) will often be diagnostic. Overproduction of immunoglobulins can lead to hyperviscosity syndrome, causing sludging of the blood in small vessels, inability to deliver oxygen, and bleeding diatheses.

References

- 1 Bergman, P. J. Paraneoplastic hypercalcemia. *Top Companion Anim Med* **27**, 156-158, doi:10.1053/j.tcam.2012.09.003 (2012).
- 2 Childress, M. O. Hematologic abnormalities in the small animal cancer patient. *Vet Clin North Am Small Anim Pract* **42**, 123-155, doi:10.1016/j.cvsm.2011.09.009 (2012).
- 3 Chisholm-Chait, A. Mechanisms of thrombocytopenia in dogs with cancer. *Comped Contin Educ Pract Vet* **22**, 1006-1017 (2000).
- 4 Withers, S. S. *et al.* Paraneoplastic hypertrophic osteopathy in 30 dogs. *Vet Comp Oncol* **13**, 157-165, doi:10.1111/vco.12026 (2015).