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PARANEOPLASTIC SYNDROMES

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PARANEOPLASTIC SYNDROMES

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Paraneoplastic syndromes (PNS) comprise a diverse group of disorders that are associated with cancer but unrelated to the size, location, metastases, or physiologic activities of the mature tissue of origin. They are remote effects of tumors that may appear as signs, symptoms or syndromes which can mimic other disease conditions encountered in veterinary medicine.

Various types of PNS, singly or in multiples, may be associated with either benign or malignant tumors and may involve almost every organ system, directly or indirectly. These disorders can precede the discovery of the tumor by weeks, months, or even years, and many are good diagnostic and prognostic indicators. The true incidence of PNS in animal cancer patients is unknown, although approximately 75% of all human cancer patients, at some time during the tumor-bearing part of their lives, suffer from one or more of these disorders.

Recognition of PNS is valuable for several reasons: (1) the observed abnormalities may represent tumor cell markers and facilitate early diagnosis of the tumor; (2) they may allow assessment of premalignant states; (3) they may aid in the search metastases; (4) they may help quantify and monitor response to therapy; and (5) they may provide insight into the study of malignant transformation and oncogene expression. Recognition of these syndromes is relevant to the diagnosis and treatment of many problems in

veterinary cancer medicine. With the increasing emphasis on diagnosis and treatment of cancer in domestic animals, PNL will be recognized, reported, and treated with greater frequency in veterinary medicine.

This review will concentrate on the pathophysiology, diagnosis, and treatment of some of the common PNS encountered in veterinary medicine.

CANCER-ASSOCIATED HYPERCALCEMIA

DEFINITION

I. Synonyms: pseudodhyperparathyroidism, malignant hypercalcemia, humoral hypercalcemia of malignancy, malignancy-associated hypercalcemia.

II. Cancer-associated hypercalcemia (CAH) is a biochemical abnormality characterized by persistent elevation of serum calcium ($\geq$ 12 mg/dl) in the presence of nonparathyroid neoplasia. It causes clinically important disturbances of function in organ systems distant from the primary tumor, sometimes resulting in severe morbidity and mortality.

III. CAH has been reported in the dog, cat, and horse in association with a variety of spontaneous neoplasms, mostly hematologic malignancies or carcinomas.

CAUSES

I. The pathogenesis of CAH is unclear. Several mediators and pathways seem to operate to produce osteolysis.

A. Direct tumor osteolysis

B. Osteolysis of prostaglandins of the E series

C. Ectopic production of peptides similar to parathyroid hormone (PTH)

D. Production of a bone-resorbing substance similar to osteoclast-activating factor (OAF)

II. Table 1 lists the neoplasms associated with CAH in domestic animals.

PATHOPHYSIOLOGY

I. Hypercalcemia may develop from several situations.

A. Bone resorption by a tumor in direct contact with bone

1. There may be localization of tumor cells and mononuclear phagocytes in bone with release of bone-resorbing factors.

2. Resorbing bone itself increases the rate of osteolysis.

B. Humorally mediated bone resorption

1. Prostaglandins of the E series may interact with macrophages to stimulate production of OAF.

a) Prostaglandins are potent local mediators of bone resorption.

b) Some hypercalcemic patients respond to prostaglandin inhibitors; this has been shown in animals with experimentally induced hypercalcemia.

2. Tumor-derived ectopic PTH directly stimulates osteoclastic bone resorption.

a) It occurs in patients without skeletal metastases and parathyroid cancer.

b) Ectopic PTH differs from native hormone.

(1) Adenylate-cyclase-stimulating protein

(2) Immunologically distinct from PTH

3. OAF is a lymphokine produced by T and B lymphocytes through a complex interaction with macrophages and prostaglandins.

II. The basic sequence of events is similar in all cases of CAH, but the degree of severity may differ.

A. Calcium accumulates despite homeostatic mechanisms such as the following that are attempting to maintain normocalcemia.

1. Increased calcitonin secretion, which inhibits bone resorption and antagonizes action of PTH
2. Increased renal excretion of filtered calcium
3. Reduced intestinal absorption
4. Reduced PTH secretion by the parathyroid glands

B. Hypercalcemia causes decreased neuromuscular function, leading to the following.

1. Weakness and sluggish response of muscles
2. Decreased electrocardiogram (ECG) QT intervals and associated cardiovascular changes
3. Gastrointestinal hypomotility
4. Central nervous system (CNS) depression and coma

C. Renal function is compromised, leading to the following.

1. Decreased ability to concentrate urine
2. Decreased glomerular filtration rate
3. Decreased renal blood flow
4. Decreased tubular reabsorption of electrolytes
5. Degeneration, necrosis, and calcification of the collecting ducts and distal convoluted tubules

6. Hypercalcemic nephropathy
7. Renal failure

CLINICAL SIGNS

I. Anorexia
II. Weight loss
III. Vomiting
IV. Muscular weakness
V. Lethargy
VI. Polyuria
VII. Polydipsia
VIII. Dehydration
IX. Depression
X. Coma, seizures (rarely)
XI. Bradycardia
XII. Cardiac dysrhythmias

DIAGNOSIS

I. Hypercalcemia cannot be diagnosed on the basis of clinical signs and physical findings alone.
II. Electrolyte imbalance may be suspected if physical findings suggest neoplasia. These findings may include the following.
   A. Bilateral or generalized peripheral lymphadenopathy
   B. Perirectal mass
   C. Abdominal mass
      1. Splenomegaly

2. Hepatomegaly

3. Mesenteric lymphadenopathy

D. Lameness

E. Poorly localized pain

F. Respiratory distress

III. A biochemical profile aids the diagnosis. Proper interpretation of total serum calcium concentrations requires adjustment of the observed calcium concentration for either serum albumin or total protein. The following calculations are valid for dogs.

A. Adjusted calcium (mg/dl)=
calcium (mg/dl) - albumin (g/dl) + 3.5

B. Adjusted calcium (mg/dl) =
calcium (mg/dl) - 0.4
(total serum protein [g/dl]) + 3.3

IV. Repeat biochemical profile within 24 hours to document persistence of hypercalcemia.

V. If the hypercalcemia is moderate to severe (>14 mg/dl), treatment of the electrolyte imbalance takes precedence over all other diagnostic procedures.

VI. Tests useful in the diagnosis of hypercalcemia include the following:

A. Biochemical tests

1. Phosphorus

Subnormal or normal concentrations suggest primary hyperparathyroidism or cancer-associated hypercalcemia.

2. Blood urea nitrogen (BUN) and creatinine

a) Normal: early hypercalcemic nephropathy

b) Elevated

(1) Widespread hypercalcemic nephropathy

(2) Primary renal disease

3. Alkaline phosphatase

a) Normal: cancer-associated hypercalcemia

b) Elevated

(1) Primary hyperparathyroidism

(2) Neoplastic osteolysis

(3) Neoplastic invasion of liver

B. Hematologic and immunologic tests

1. Complete blood count (CBC) may reveal atypical lymphocytes with lymphoma or lymphocytic leukemia.

2. Serum protein electrophoresis showing a monoclonal spike in the beta and gamma region(s) usually reflects lymphocytic neoplasia or a lymphoproliferative disorder.

C. Radiographic examination

1. Skeletal survey

a) Neoplastic osteolysis

b) Multiple myeloma

(1) "Punched-out" lesions

(2) Pathologic fractures

c) Degree of skeletal demineralization

(1) Mild

i) Cancer-associated hypercalcemia

ii) Primary hyperparathyroidism

(2) Moderate to severe

i) Chronic renal disease

ii) Nutritional hyperparathyroidism

2. Thorax

a) Mediastinal mass

b) Enlarged thoracic lymph nodes

c) Pulmonary metastasis

3. Abdomen

a) Hepatosplenomegaly

b) Enlarged abdominal lymph nodes

c) Abdominal mass

D. Urinalysis

1. Low urine specific gravity

2. Hypercalciuria

a) Qualitative method based on turbidity

b) Quantitative method based on 24-hour collection

3. Bence-Jones proteinuria

E. Biopsy (of suspected lesion)

1. Excisional or incisional biopsy

2. Aspiration cytology

3. Bone marrow aspiration or biopsy

F. ECG examination

VII. If the diagnostic procedures listed above fail to identify the cause of the hypercalcemia, the following procedures can be attempted.

A. Corticosteroid challenge test

1. Prednisone or prednisolone, at a dosage of 2-3 mg/kg body weight (or 40 mg/m^2 body surface area), is given orally every 12 hours.
2. Recheck the calcium concentration 3-5 days after start of medication.
3. Animals with cancer-associated hypercalcemia often have moderately or markedly reduced serum calcium concentration; those with other causes do not.

B. Laparotomy and biopsy

C. Surgical exploration of neck

D. Determination of PTH concentration by radioimmunoassay

E. Determination of prostaglandin E_2 concentration by radioimmunoassay

DIFFERENTIAL DIAGNOSIS

I. Growth in young animals: may be associated with transient hypercalcemia

II. Primary hyperparathyroidism

III. Hypervitaminosis D

IV. Primary renal disease

A. Chronic renal disease

B. Diuretic phase of acute renal failure

V. Hyperproteinemia (hemoconcentration)

VI. Hypoadrenocorticism

VII. Septic osteomyelitis

VIII. Disuse osteoporosis

IX. Laboratory error

TREATMENT

I. Reduce the serum calcium concentration; treatment is tailored to fit the degree of hypercalcemia and clinical condition of the animal.

A. For mild hypercalcemia (12-14 mg/dl)

1. Sodium phosphate 1-3 g, diluted with water to 10-20 ml PO
2. NaCl 0.9% 20-30 ml/kg/day IV

B. For moderate hypercalcemia (14-16 mg/dl)

1. NaCl 0.9% 30-45 ml/kg/day IV
2. Furosemide 1-3 mg/kg IV SID-BID
3. Prednisone 2-3 mg/kg PO BID
4. For dehydrated animals, sterile Ringer's lactate solution alternated with normal saline IV

C. For hypercalcemic crisis (>16 mg/dl) with oliguric renal failure

1. Alternating liters of 0.9% NaCl and Ringer's lactate solution IV
2. Osmotic diuresis with 10% dextrose/water (D/W) IV and/or peritoneal dialysis
3. Sodium bicarbonate IV

D. Additional treatments

1. Calcitonin 4-8 U/kg IM, SQ SID-BID
2. Diphosphonates 10-30 mg/kg PO BID-TID
3. Mithramycin 02.5 μg/kg IV SID once or twice
4. EDTA 25 - 75 mg/kg/h IV cautiously
5. Gallium nitrate 100 mg/m^2 or 2.5 mg/kg IV SID x 5 days
6. Interferon (Chew and Carothers, 1989)
7. Calcitonin suppositories with single infusion of biphosphonate (Thiebaud et al., 1990)

II. Once the serum calcium concentration is restored to normal, treatment of the underlying malignancy is mandatory.

PATIENT MONITORING

I. Major complications include the following.

A. Oliguric renal failure

B. Acid-base/electrolyte disorders

C. Sepsis

D. Reaction to anticancer therapy

II. Serum calcium, BUN, creatinine, and urine production should be monitored daily in patients with moderate to severe renal dysfunction.

III. Parenteral administration of fluids and drugs is continued until the patient is able to retain liquids and foods.

IV. Broad-spectrum antibiotic support is considered as these patients are usually immunosuppressed.

V. Response to anticancer therapy is monitored through regular determinations of serum calcium concentration.

VI. Serum calcium determinations should continue on a regular basis (monthly) while the cancer is in apparent remission, as hypercalcemia can recur weeks or months before relapse.

VII. Owners should be warned of the poor prognosis associated with the syndrome.

EXTRAPANCREATIC TUMOR HYPOGLYCEMIA

DEFINITION

I. Extrapancreatic tumor hypoglycemia (EPTH) constitutes an important biochemical abnormality characterized by significant fasting hypoglycemia (<60 mg/dl) in the presence of non-islet-cell tumors. It can cause neuroglycopenic symptoms in affected animals that are indistinguishable from those that occur with islet cell tumors (insulinoma). Neuroglycopenic refers to CNS symptoms caused by low blood glucose.

II. The syndrome has been attributed to several malignant conditions of varying cell types in the dog and cat, most commonly hematologic malignancies or carcinomas (Table 2).

CAUSES

The pathogenesis of EPTH, unlike that of islet cell tumors, is unclear. Several processes may be involved.

I. Secretion of insulin or insulin-like substances

A. Ectopic insulin that is immunologically similar to native insulin

B. Nonsuppressible insulin-like activity

II. Insulin receptor proliferation

III. Excessive utilization of glucose by the tumor

IV. Failure of compensatory mechanisms

A. Inhibition of glycogenolysis or gluconeogenesis

B. Destruction of the liver by tumor metastases

C. Suppression of the secretion of counterregulatory hormones

PATHOPHYSIOLOGY

I. Regardless of cause, neuroglycopenic symptoms of cerebral dysfunction predominate.

A. Usually do not develop until blood glucose falls below 40-50 mg/dl

B. Mimic a wide variety of metabolic and neurologic disorders

II. Neuroglycopenic symptoms are directly related to the rate at which blood glucose falls rather than to the degree of hypoglycemia.

A. Onset, severity, and duration of symptoms can vary with the following external stimuli.

1. Fasting

2. Eating

3. Exercise

4. Excitement

B. Symptoms can vary according to the specific derangement in the glucose homeostatic mechanisms.

III. Because glucose is the sole fuel source of the brain, certain reactions occur.

A. Brain areas with high metabolic rate (especially the cortex) are affected initially, then the metabolically slower vegetative centers.

B. Neurologic signs occur rapidly because there is only limited carbohydrate reserve in neural tissue.

IV. Hypoglycemia induces release of counterregulatory hormones.

A. Catecholamines

B. Cortisol

C. Glucagon

D. Growth hormone

V. Prolonged hypoglycemia may cause the following:

A. Hypoxic damage to cerebral cortex and lower centers

B. Irreversible damage with neuronal degeneration

C. Death, by depression of the respiratory center

CLINICAL SIGNS

I. Disorientation

II. Weakness

III. Hunger

IV. Anorexia

V. Nervousness

VI. Convulsions

VII. Coma

DIAGNOSIS

I. History suggests hypoglycemic episodes.

II. It is usually a diagnosis of exclusion; rule out all other causes of fasting hypoglycemia.

III. Tumors associated with EPTH are often large and produce signs and symptoms caused by a space-occupying lesion.

A. Intrathoracic tumors

1. Dyspnea

2. Cough

3. Chest pain

B. Retroperitoneal tumors

1. Abdominal distension

2. Palpable mass

3. Ascites

IV. Radiograph the thoracic and abdominal cavities.

V. Perform a biochemical profile to document fasting hypoglycemia.

VI. Repeat sampling if blood glucose is 60 mg/dl.

A. Submit for both glucose and insulin assays.

B. Suspect animals may need to be fasted for 24-48 hours.

VII. Determine amended insulin-glucose ration (AIGR).

A. It discriminates between insulinoma and other causes of hypoglycemia.

B. Formula is as follows.

$$\frac{\text{Serum insulin } (\mu U/ml \times 100)}{\text{Serum glucose (mg/dl)} - 30} = \text{AIGR}$$

C. An AIGR of >30 is diagnostic for insulinoma.

VIII. Provocative testing may be useful.

A. Glucagon tolerance test

B. Intravenous glucose tolerance test

C. Oral glucose tolerance test

IX. Perform tumor biopsy.

X. Perform exploratory laparotomy.

DIFFERENTIAL DIAGNOSIS

Extrapancreatic tumor hypoglycemia must be differentiated from other causes of hypoglycemia and neuroglycopenic symptoms.

TREATMENT

I. Nonspecific therapy for hypoglycemia

A. Frequent feedings

B. Hyperglycemic agents; dosages for dogs:

1. Diazoxide 5-13 mg/kg PO BID-TID

2. Hydrochlorothiazide 2-4 mg/kg PO BID to supplement diazoxide

3. Prednisone 10-20 mg PO BID

4. Glucagon 0.03 mg/kg IV

5. Propranolol 10-40 mg PO TID

6. Phenytoin 6 mg/kg PO BID-TID

C. Glucose-containing solutions PO, IV

II. Specific therapy directed toward the tumor

A. Surgery

B. Chemotherapy

C. Radiation therapy, etc.

PATIENT MONITORING

I. Monitor blood glucose at least every 2 weeks after tumor-specific therapy.

II. Watch for recurrence of neuroglycopenic signs and symptoms.

III. Watch for evidence of tumor recurrence and relapse.

IV. Warn owner of the likelihood of recurrence of tumor and associated hypoglycemia.

ANOREXIA-CACHEXIA COMPLEX

DEFINITION

I. Anorexia-cachexia complex refers to a phenomenon characterized by severely reduced or nearly complete cessation of spontaneous food consumption. It manifests as progressive emaciation and debility.

II. Cachexia may also occur in the absence of anorexia from profound alterations in host metabolism.

III. The complex is a common finding in most animal cancer patients at some time during the course of their illness.

CAUSES

I. Anorexia

A. Altered odor or taste perception

B. Substances associated with anorexia

1. Lactate
2. Ketones
3. Tumor-derived or tumor-induced circulating factors
   a) Tumor necrosis factor
   b) Interleukin-1 α

C. Direct effects of the tumor on the appetite center

D. Modification of eating behavior by an aberrant metabolic compound

II. Cachexia

A. Anatomic alterations

B. Imbalance between caloric intake and expenditure
   1. Inadequate food ingestion
   2. Impaired digestion and absorption
   3. External nutrient loss
   4. Tumor-host competition for nutrients
   5. Increased energy expenditures by the host

C. Altered metabolism of glucose and other fuel sources
   1. Basal metabolic rate increased despite caloric deficit
   2. Increased Cori cycle activity (lactate metabolism) resulting in increased energy expenditure
   3. Glucose intolerance with marked resistance to insulin and abnormal insulin production
   4. Altered protein synthesis and catabolism
   5. Decreased anabolic enzymes, increased catabolic enzymes
   6. Factors implicated in altering metabolism

a) Tumor necrosis factor

b) Interferons/interleukins

c) Prostaglandin E_2

d) ACTH-like hormone

e) Altered thyroid homeostasis

PATHOPHYSIOLOGY

I. The syndrome often begins with anorexia and decreased absorption of nutrients.

II. Hypermetabolism, and host deletion of stored calories occur early in the process.

III. Profound alterations occur in organ structure and function, resulting in cachexia and increased morbidity.

IV. No direct relation exists between degree of cachexia and caloric intake, tumor burden, tumor cell type, or anatomic site of involvement.

CLINICAL SIGNS

I. Early satiety

II. Anorexia

III. Weight loss

IV. Anemia

V. Marked debility

DIAGNOSIS

I. There is a history of weight loss and poor appetite.

II. Evidence of neoplasia may be obvious on physical examination.

III. Thoracic and abdominal radiographs may reveal masses with or without metastatic disease.

IV. Cytology or biopsy allows definition of histologic cell type of suspect lesions.

DIFFERENTIAL DIAGNOSIS

I. Starvation

II. Heavy parasitic infestation

III. Endocrine disorders

A. Hypoadrenocorticism

B. Hyperthyroidism

C. Hypopituitarism

IV. CNS lesions, especially diencephalic syndrome

V. Chronic infectious diseases

A. Feline infectious peritonitis (FIP)

B. Systemic mycosis

VI. Malabsorption/maldigestion syndromes

TREATMENT

I. Criteria for dietary supplementation

A. Oral intake (calories and protein) <80% of recommended

B. Albumin <2.5 g/dl

C. Presence of stomatitis or gastrointestinal abnormalities

D. Weight loss >5% of usual weight

E. Fever or sepsis

II. Dietary rehabilitation

A. Special oral diets and nutrients

a) Protein 4-6 g/kg/day;high biologic value

b) Fat 1.3 g/kg

c) Carbohydrate 10.1 g/kg

d) Calories 70-110 kcal/kg/day

e) Vitamin supplementation should be considered

B. Tube feedings

C. Parenteral nutrition, partial or total

III. Enhancing palatability of food

A. Warm the food.

B. Flavor the food with meat or animal fat.

C. Increase olfactory stimulation with small amounts of onion or garlic.

D. Divide diet into small multiple feedings.

IV. Anabolic agents: questionable efficacy

V. Appetite stimulants

A. Diazepam (cat) 0.05-0.15 mg/kg IV SID, QOD

B. Oxazepam (cat) 0.2-0.5 mg/kg PO SID-BID

VI. Specific anticancer therapy

PATIENT MONITORING

I. Weigh patient weekly.

II. Weigh food portions and record daily intake.

III. Watch for progressive emaciation.

IV. Monitor hematologic profile for onset of anemia with a CBC every other week.

V. Monitor albumin and total protein concentration with a biochemical profile once monthly.

VI. Consider these cautions.

A. Parenteral dietary rehabilitation can have adverse metabolic consequences.

B. Anticancer therapies can adversely affect existing anorexia/cachexia.

VII. Warn owners that marked cachexia entails a poor prognosis.

FEVER OF UNKNOWN ORIGIN

DEFINITION

I. Fever of unknown origin (FUO) is characterized by a continuous or intermittent temperature of 39.7°C (103°F) or greater that lasts 3 weeks or longer and remains undiagnosed after 1 week of in-hospital evaluation.

II. Fever is a common presenting sign in dogs and cats with neoplasia.

CAUSES

I. Neoplastic disorders implicated in the dog and cat include the following.

A. Lymphoma, especially with hepatic involvement

B. Leukemia, myeloma, myeloproliferative disorders

C. Intracranial tumors

D. Hepatic tumors

E. Mastocytoma

II. FUO may be associated with any neoplasm undergoing active necrosis or secondarily infected.

PATHOPHYSIOLOGY

I. Neoplasms may provide sources of endogenous pyrogen.

II. Interaction of tumor-specific or tumor-related antigens with sensitized lymphocytes may induce fevers.

A. Lymphocytes release a lymphokine.

B. Lymphokine stimulates production of an endogenous pyrogen by neutrophils or macrophages.

CLINICAL SIGNS

I. Persistent fever

II. Weight loss

III. Dehydration

IV. Anorexia

V. Lethargy

DIAGNOSIS

I. Complete a history and physical examination, looking for neoplasia.

II. Record rectal temperature two or three times a day to document persistence of fever.

III. Perform routine diagnostic tests.

A. CBC, urinalysis

B. Serum biochemical profile

C. Thoracic and abdominal radiographs

IV. Rule out other causes of FUO with the following.

A. ECG, echocardiography

B. Upper and lower gastrointestinal contrast studies

C. Radiographic skeletal survey

D. Aerobic and anaerobic blood cultures

E. Arthrocentesis of multiple joints

F. Serologic tests for immune-mediated diseases, systemic mycoses, and rickettsial, bacterial, and viral diseases

G. Excretory urography

H. Abdominal ultrasonography

V. Employ invasive diagnostic procedures if fever persists and physical and laboratory findings suggest a disease process that cannot otherwise be adequately evaluated.

A. Fine-needle aspiration cytology

B. Biopsy: bone marrow, lymph node, liver, bone, bowel

C. Laparotomy

TREATMENT

I. Consider nonspecific therapy, usually based on the use of antiprostaglandin compounds.

A. Salicylates (aspirin)

1. Dogs: 10 mg/kg PO BID

2. Cats: 6 mg/kg PO q 48-52 h

B. Dipyrone 0.20-0.25 ml/5 kg IM, SQ BID-QOD

II. Primary therapy for fever of neoplastic disease without infection is directed toward the neoplasm.

III. Prophylactic antibiotic therapy is appropriate for leukopenic patients or those with inflamed, necrotic, and secondarily infected neoplasms.

PATIENT MONITORING

I. Take rectal temperatures and record once daily.

II. Perform CBC every 2 weeks to monitor for leukopenia or evidence of sepsis.

III. Weigh patient once a week.

IV. Watch for complications of existing leukopenia or infection.

V. Watch for evidence of tumor recurrence.

Table 1. NEOPLASMS ASSOCIATED WITH HYPERCALCEMIA IN DOMESTIC ANIMALS

Site	Neoplasm
Lymphoid tissue	Lymphoma (lymphosarcoma) Lymphocytic leukemia Multiple myeloma Thymoma
Skin and soft tissue	Adenocarcinoma of the apocrine glands of the anal sac Fibrosarcoma
Abdominal cavity	Gastric carcinoma Adenocarcinoma of the exocrine pancreas
Respiratory system	Epidermoid carcinoma Nasal adenocarcinoma
Reproductive system	Mammary gland adenocarcinoma Interstitial cell tumor Seminoma
Skeletal system	Primary bone tumors Metastatic bone tumors

Table 2. NEOPLASMS ASSOCIATED WITH EPTH IN THE DOG AND CAT

Lymphoma (lymphosarcoma)
Lymphocytic leukemia
Plasma cell dyscrasia
Primary pulmonary carcinoma
Metastatic mammary carcinoma
Hepatoma
Hepatocellular carcinoma
Hemangiosarcoma
Leiomyosarcoma

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