PARANEOPLASTIC SYNDROMES IN THE DOG AND CAT

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PARANEOPLASTIC SYNDROMES

- All signs not related to the physical presence of the tumor mass, These indirect effects result from the production and release of biologically active substances including
  - Hormones
  - Growth factors
  - Cytokines
- PNS are:
  - Unrelated to size or location of the primary tumor
  - Unrelated to presence/absence of metastases
  - Maybe present before the actual tumor mass is noted
  - May serve as a tumor marker

The chance that a cancer–patient is brought to the clinic for PNS rather than the actual tumor is high

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PARANEOPLASTIC SYNDROMES

Constitutional
- Weight loss/Cachexia
- Fever
- Hyperviscosity
- Hypertrophic osteopathy

Cutaneous
- Nodular dermatofibrosis
- Superficial necrolytic dermatitis
- Pemphigus vulgaris
- Alopecia

Neurologic
- Myasthenia gravis
- Neuropathy

Gastrointestinal
- GI-ulceration
- Diarrhea

Secondary auto-imune/immune-mediated disease

Hematologic
- Anaemia
- Polycythemia
- Leukocytosis (neutrophilia; eosinophilia)
- Thrombocytosis
- Pancytopenia

Coagulation disturbances
- Thrombocytopenia
- Thrombocyopathy
- DIC

Metabolic
- Hypercalcemia
- Hypoglycemia
- Hyperhistaminemia
- Hypokalemia

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What is the PNS most commonly associated with cancer by owners?

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DUSHI – DSH FN 15Y

Has received multiple surgeries for mammary gland masses (nodulectomies) with no histopathology performed

Owner recently noted:
- Weight loss
- Progressive loss of appetite
- Otherwise fine

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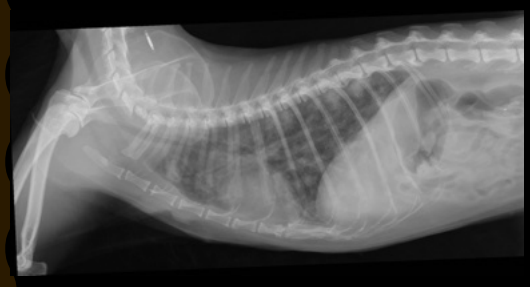
THORACIC RADIOGRAPHS



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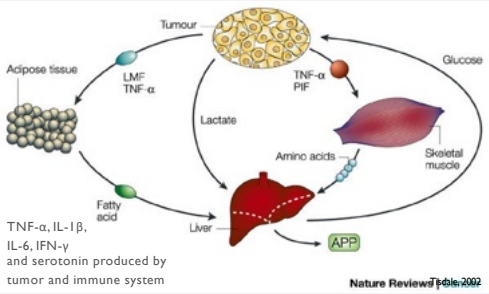
CANCER CACHEXIA MEDIATORS



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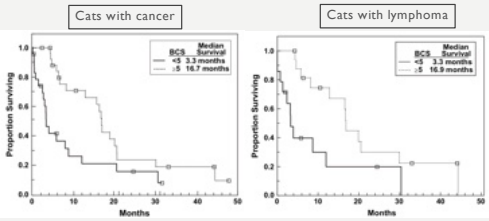
CANCER CACHEXIA

Has a significant effect on the patient:

- Decreases quality of life
- Decreased function immune-system
- Leads to a poorer response to treatment
- Shorter survival



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CANCER CACHEXIA

1. Altered carbohydrate metabolism
   - Anaerobic glycolysis of glucose in tumor cells
   - Relative insulin resistance (higher insulin levels)
2. Protein breakdown higher than protein synthesis
   - Muscle wasting, decreased immune and GI-function, poor wound healing
   - PIF (Proteolysis Inducing Factor)
3. Increased lipolysis and decreased lipogenesis
   - Due to changes in lipoprotein lipase and/or peripheral insulin resistance
   - Tumors have limited ability to use lipids for energy

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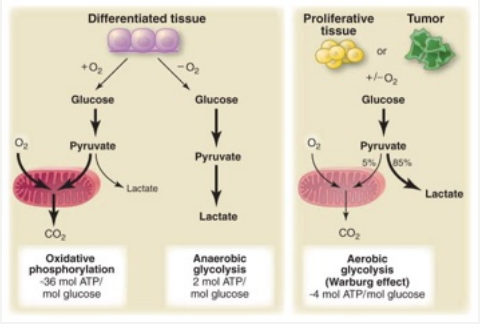
CANCER CACHEXIA
WARBURG EFFECT



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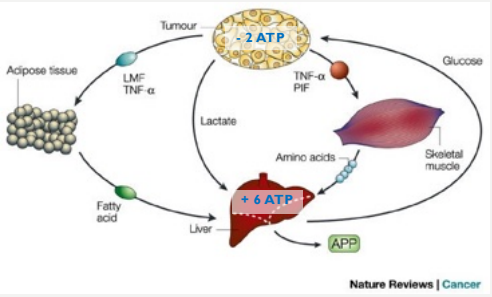
CANCER CACHEXIA
CORI CYCLE



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CANCER CACHEXIA - TREATMENT

Multimodal approach essential in order to achieve maximum effect!

1. Treat the cancer (if possible)
2. Reduce adverse events anti-cancer therapies
3. Reduce inflammatory response
4. Dietary interventions
   - Optimize diet
   - Supplements
   - Additional feeding
   - Assisted feeding / Feeding tubes

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CANCER CACHEXIA - DIET

Theoretical "ideal" dietary requirements:

- Highly palatable
- Highly digestible
- High in energy content
- High In Fat
- Low in Carbohydrates (Ringer's lactate myth)
- Low in Proteins
- Additional omega-3 fatty acids (EPA/DHA)?

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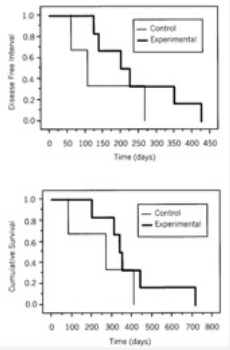
CANCER CACHEXIA



Dogs with multicentric lymphoma treated with doxorubicin and "ideal" diet:

1. Beneficial effect on DFP and survival
2. More rapid decline circulating cytokine levels
3. Reduced insulin resistance & hyperlactatemia

median: 107 days; 75th quantile: 209 days; 25th quantile: 63 days). Dogs fed the experimental diet had numerically ($P = 0.23$) greater mean ± SE (318.6 plusmn; 57.6 days), median (319 days), 75th quantile ST (440 days), and 25th quantile ST (124 days) compared with the dogs fed the control diet (mean ± SE: 227.6 ± 42.1 days; median: 232 days; 75th quantile: 388 days; 25th quantile: 94 days) (Table 4). Stratifica-

Ogilvie et al, Cancer, 2000:
Effect of fish oil for dogs with lymphoma:

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WHAT IS THE MOST COMMON PNS ASSOCIATED WITH CANCER?

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ANEMIA

- Variable degree of anemia, typically mild to moderate
- Often multifactorial
- Signs may vary depending on degree of anemia and rate of onset

Anemia	
Regenerative	*Non-regenerative*

• Blood loss
• Hemolysis
  • Immune-mediated
  • Non-immune-mediated
  • Infectious
  • Hypophosphatemia
  • Heinz body anemia
  • Hemophagocytic syndrome
  • Microangiopathic hemolysis
	• Acute blood loss
	• Anemia of chronic disease
	• Endocrine dysfunction (EPO, T4, cortisol)
	• Deficiency: (relative) iron, protein, vitamins
	• Immune-mediated destruction of erythroid precursors (e.g. PRCA)
	• Myelopthisis
	• FeLV

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ANEMIA IN CANCER PATIENTS

1. **Anemia of chronic disease**
   - typically mild, normocytic-normochromic, non-regenerative
   - relative iron-deficiency, (hepcidin) reduced life-span erythrocytes
2. **Myelophthysis**
   - non-regenerative
   - often bi-/pancytopenia
3. **Blood loss anemia**
   - microcytic, hypochromic, hypo-/non-regenerative
   - mast cell tumors, intestinal tumors, gastrinomas,
4. **Immune-mediated hemolytic anemia** (spherocytes)
   - Regenerative
   - haematopoietic tumors (malignant lymphoma)
5. **Microangiopathic hemolytic anemia** (schistocytosis)
   - Hemangiosarcomas, DIC

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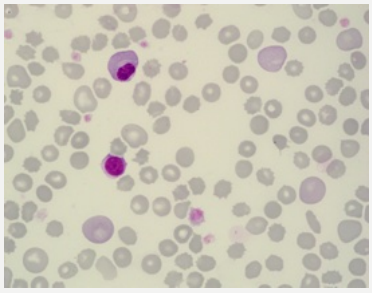
ANEMIA



Spherocytes, anisocytosis, polychromasia, nucleated red blood cells
Immune-mediated hemolytic anemia

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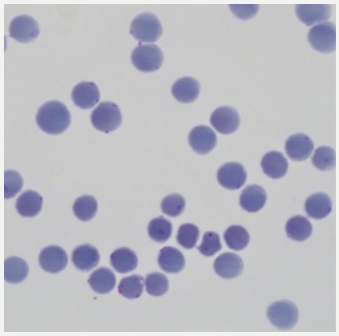
ANEMIA



Secondary infections incl. *Mycoplasma spp hemofelis*

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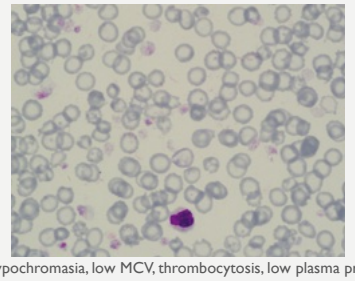
ANEMIA



Hypochromasia, low MCV, thrombocytosis, low plasma proteins
Chronic gastro-intestinal blood loss (iron deficiency)

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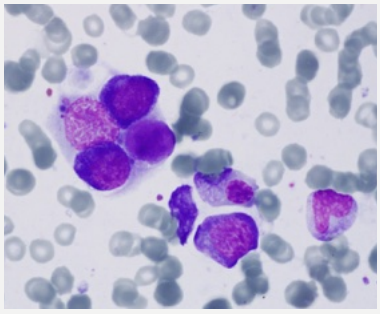
ANEMIA



Bone marrow - Phagocytosis erythroid precursors

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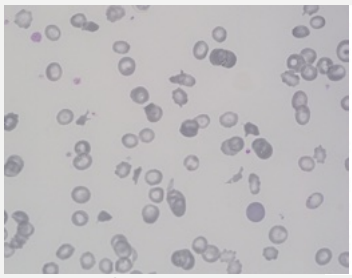
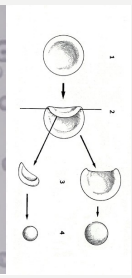
ANEMIA





Schistocytes, acanthocytes, thrombocytopenia,
nucleated red blood cells
Microangiopathic hemolysis (splenic hemangiosarcoma)

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WHAT IS THE BEST KNOWN PNS ASSOCIATED WITH CANCER?

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YULA - SWISS WHITE SHEPHERD, F, 8Y6M

- Presenting signs: Itching and licking around tail/anus.
- Referring vet:
  - Anal sac problem?
  - PE: small mass (<1cm) in left anal sac
  - Cytology: consistent with apocrine anal sac adenocarcinoma
- Surgery: marginal excision L-sided anal sac carcinoma

- Referred for post-operative radiotherapy
  - Rectal examination: no palpable mass
  - US abdomen and thoracic radiographs: unremarkable
  - Total calcium: 3.76 mmol/L (Ref: 1.98-2,97 mmol/L)

- So what's next?

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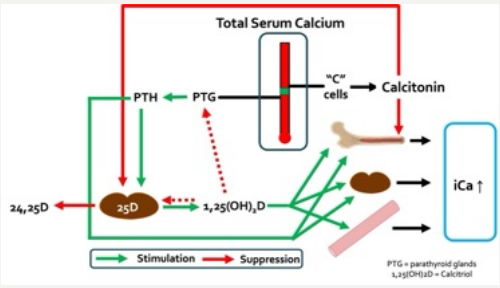
CALCIUM REGULATION



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HYPERCALCEMIA

1. **Laboratory error**

2. **Non-neoplastic causes**
   - Renal failure (renal secondary hyperparathyroidism)
   - Dietary (nutritional secondary hyperparathyroidism)
   - Hypervitaminosis D (rodenticides, plants, dietary oversupplementation)
   - Addisonian's disease / hypoadrenocorticism
   - Granulomatous inflammation (vitamin D analogues)
   - Idiopathic (cat)

3. **Neoplastic causes**
   - Primary hyperparathyroidism (PTH)
     Parathyroid hyperplasia/adenoma/carcinoma
   - Humoral Hypercalcemia Malignancy (PTH-rp)
     T-cell lymphoma, anal sac carcinoma, mammary carcinoma, hepatocellular carcinoma, other carcinomas, thymoma, histiocytic sarcoma
   - Osteoclast Activating Factors (OAF's: IL-1, TNFα)
     Multiple myeloma, B cell lymphoma
   - Osteolytic tumors (primary or secondary)
     Incl. osteosarcoma, feline squamous cell carcinoma, bone metastases

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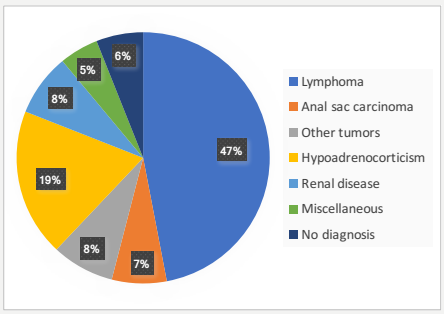
HYPERCALCEMIA - DOG CAUSES



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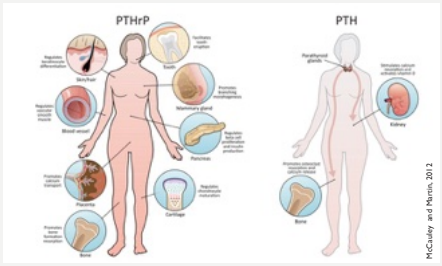
PTH-RP



- Produced in many primitive neuroendocrine tissues and placenta
- Wide variety of activities due to processing of precursor into multiple hormones and the use of multiple receptors
- Endocrine (3), paracrine (mostly) and autocrine function

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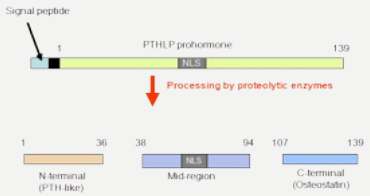
PTH-RP



- PTHrp is a protein polyhormone:
  - N-terminal region: 70% homology with PTH; binds and stimulates PTH receptors in bone/kidney, to lower extent 1,25-dihydroxyvitamin D production
  - Midregion: stimulation Ca-uptake placenta
  - C-terminal region: can inhibit osteoclastic bone resorption
- Human PTHrP N-terminal RIA can be used in the dog and cat

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HYPERCALCEMIA DIAGNOSIS

1. Start with
   - Blood: total Ca (if available iCa^{2+}), PO_4, albumin, kidney function
   - Urine: s.g.
   - Repeat calcium!!
2. Look for cancer
   - Physical examination.: lymph nodes (incl. cytology), rectal exam
   - Imaging: thoracic radiographs; abdominal US ± parathyroids
   - Bone marrow
3. May need to consider
   - PTH/PTH-rp/$VitD_3$

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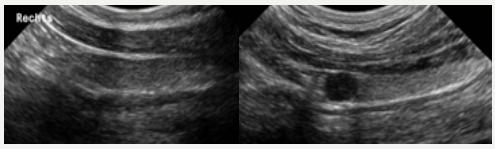
YULA

	Result	Reference Range
Calcium	4.56 mmol/L	1.98-2,97
Albumin	34 g/L	26-37 g/L
Urea	5,1 mmol/L	3,0-12,5
Creatinin	99 umol/L	50-129
PTH	133 pg/mL	
PTH-rp	< 0.1 pmol/L	



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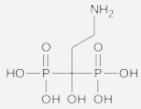
HYPERCALCEMIA - TREATMENT

- Identify cause!!!!!
- Correct dehydration and start diuresis
  - Calcium-free fluids - 0.9% NaCl preferred
- Diuretics
  - Furosemide; rarely necessary
    - only after correction hypovolemia!
- Biphosphonates (Pamidronate)
- Salmon calcitonin
- Mithramycin
- Glucocorticoids



Steroids should only be used **after** a diagnosis has been made or all diagnostic samples have been secured!

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PARANEOPLASTIC CUTANEOUS SIGNS

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PARANEOPLASTIC - CUTANEOUS

Symmetric alopecia due to hyperestrogenism
Sertoli cell tumor

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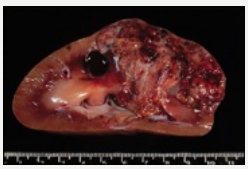
PARANEOPLASTIC - CUTANEOUS



Nodular dermatofibrosis
Bilateral renal cystadenocarcinomas
Genetic disorder in German shepherd dog

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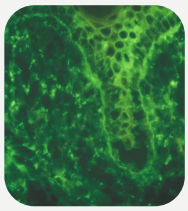
PARANEOPLASTIC - CUTANEOUS



Mucocutaneous eruptions with blisters/erosions
Paraneoplastic pemphigus

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PARANEOPLASTIC - CUTANEOUS

Superficial necrolytic dermatitis*
Glucagonoma

- Rare condition, usually older dogs
- Progressive skin lesions (weeks to months)
- Pathogenesis unclear
  - Associated with glucagonomas, chronic hepatic disease, DM
- Low plasma amino-acid concentrations (30% of normal)
  - Humans: low zinc and essential fatty acids

*a.k.a Necrolytic Migratory Erythema or hepatocutaneous syndrome

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PARANEOPLASTIC – CUTANEOUS
SUPERFICIAL NECROLYTIC DERMATITIS

Signs
- Cutaneous lesions:
  - erythema, crusting, ulceration, alopecia
  - marked crusting and ulceration of footpads
- Facial area/oral cavity, *pressure points*, perianal region
- Secondary infections common

Diagnosis
- Histologic skin biopsy

Therapy:
- Treat primary disease
- Supportive treatment
  - Antibiotics
  - Dietary protein supplementation with egg-yolk or high-quality protein
  - Amino acids infusions

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DUNCAN – DSH MN 7Y

Progressive non-pruritic skin lesions

Bloodwork: normal
FeLV/FIV: negative
Fungal culture: no growth
Skin scraping: no parasites

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DUNCAN

Dermatology service
Nonpruritic scaling, diffuse erythema, and alopecia,
mostly on the head and pinnae in an otherwise healthy cat

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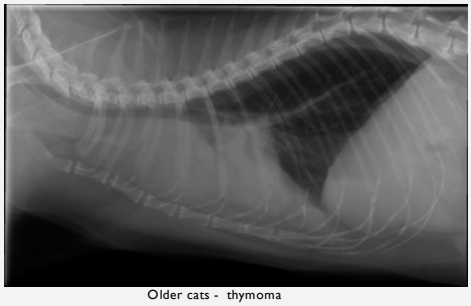
DUNCAN – DSH MN 7Y



Older cats - thymoma
Feline exfoliative dermatitis

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FELINE EXFOLIATIVE DERMATITIS

Signs
- Cutaneous lesions
  - generalized exfoliation, scales, and crusts
  - alopecia
  - non- to mildly pruritic
- Systemic signs: lethargy, anorexia, and weight loss for several weeks

Causes
- Thymoma
- Non-thymic neoplasms, drug administration, nutritional factors

Diagnosis
- Histologic skin biopsy: interface dermatitis, mural interface folliculitis, sebaceous adenitis

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HUMMIE – DSH FN 11Y

Systemic signs
- lethargy
- abdominal distension

Skin
- progressive, diffuse, symmetrical alopecia
- Thin, greasy and glistening skin
- Fissured footpads

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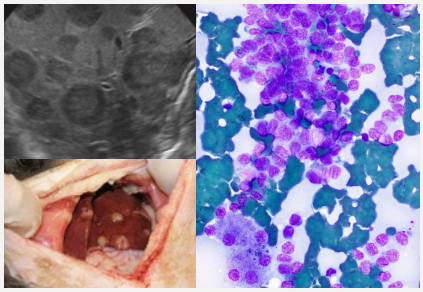

Associated with pancreatic or hepatic/bile duct carcinoma
Feline paraneoplastic alopecia

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BRUCE – ROTTWEILER MN 8Y

Since 2 weeks
- Progressive lameness
- Thickened, painful distal limbs
- Loss of appetite
- Occasional cough

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HYPERTROPHIC OSTEOPATHY

Typically (large) thoracic or abdominal mass

Signs
- (sub)acute onset (<3W)
- Lameness with (symmetrical) limb swelling
- Ocular discharge, episcleral injection, lethargy

Diagnosis
- Rx limb: periostal reaction of distal long bones
- Mass: metastatic > primary; thorax > abdomen
- Anemia, neutrophilia elevated ALP

Treatment
- Treat underlying condition
- Neurotomy vagal nerve

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HYPERTROPHIC OSTEOPATHY

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HYPERTROPHIC OSTEOPATHY

Musée Fragonard de l'École vétérinaire de Maisons-Alfort (Paris, France)

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WHAT'S YOUR DIAGNOSIS?

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