

Paraneoplastic Syndromes

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Overview

- Hypercalcemia
- Anemia and thrombocytopenia
- Hypertrophic osteopathy (HO)
- Miscellaneous
 - Hypoglycemia
 - Fever
 - Erythrocytosis
 - Myasthenia gravis

Paraneoplastic Syndromes (PNSs)

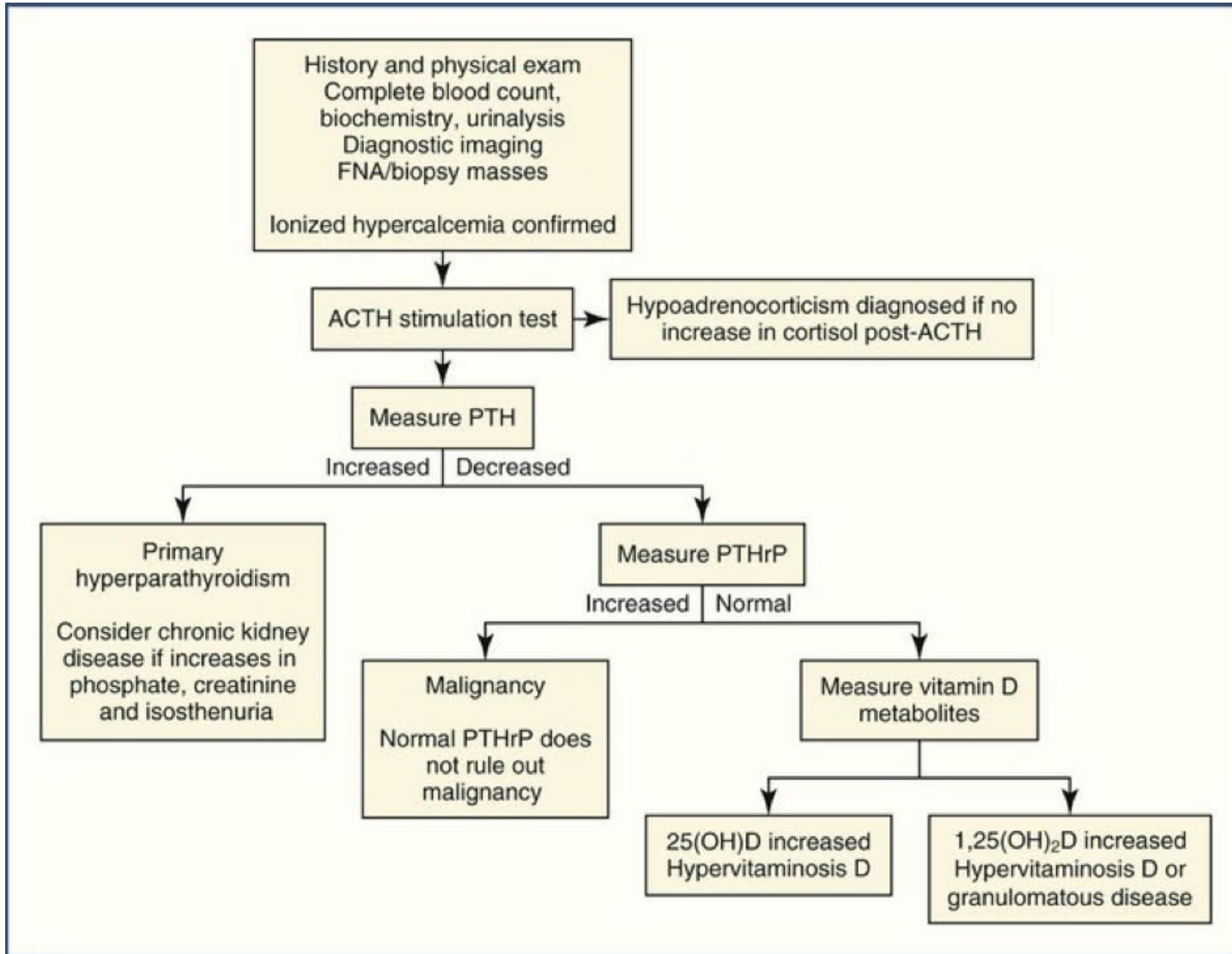
“cancer-associated alterations in bodily structure and/or function that are not directly related to the physical effects of the primary or metastatic tumor”

- Usually caused by
 - Tumor production of small molecules - hormones, cytokines, peptides
 - Tumor depletion of normal small molecules
 - Host responses to the tumor – usually immune mediated

Hypercalcemia

Hypercalcemia

- Neoplastic cause in 60% of dogs and 30% of cats with hypercalcemia
- Differential Diagnoses
 - Dogs
 - Primary hyperparathyroidism
 - Chronic kidney disease
 - Hypoadrenocorticism
 - Hypervitaminosis D
 - Granulomatous disease
 - Cats
 - Idiopathic
 - Chronic Kidney disease

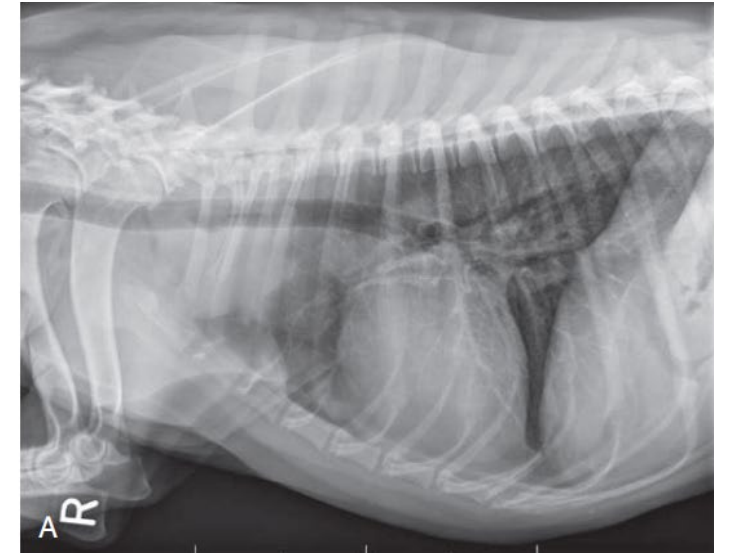


- Ionized calcium, parathyroid hormone (PTH) and parathyroid related peptide (PTHrp)
- Hypercalcemia of malignancy (HM) often mediated by PTHrp but not always
 - Normal PTHrp level does not rule out cancer
- Other mediators of HM
 - IL-1, IL-6, TNF, calcitriol

Hypercalcemia of Malignancy Panel

Hypercalcemia of Malignancy (HM)

- Dogs
 - T-cell lymphoma
 - 35-55% of dogs with T-cell lymphoma
 - Anal sac apocrine gland adenocarcinoma
 - 25% of dogs with AGASACA
 - Multiple Myeloma
 - Melanoma
 - Thymoma
- Cats
 - Lymphoma
 - Squamous cell carcinoma
 - Multiple Myeloma



HM – T-Cell LSA

Poll Question #1

Aside from PTHrp, what is another common mediator of hypercalcemia of malignancy?

- A. Interferon-gamma
- B. IL-1
- C. Calcitonin
- D. TGF-beta

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HM Management

- Treat the underlying disease
 - Lymphoma
 - CHOP, T-cell LSA shorter response duration and MSTs
 - AGASACA
 - Surgery
 - Palladia¹
 - Radiation therapy
 - Resolution in 31% w/ RT alone, additional 46% in dogs with RT + prednisone and bisphosphonates²

1. London, C et al.: Preliminary evidence for biologic activity of toceranib phosphate (Palladia®) in solid tumours, *Vet Comp Oncol* 10: 194-205, 2012.

2. McDonald C, Looper J, Greene S: Response rate and duration associated with 4Gy 5 fraction palliative radiation protocol, *Vet Radiol Ultrasound* 53:358-364, 2012.

• BOX 5.2 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

Fluid therapy with 0.9% NaCl—rehydrated with subcutaneous or intravenous treatment

Moderate to Severe Hypercalcemia and Clinical Signs

Fluid therapy with 0.9% NaCl—correct dehydration over 4 to 6 hours, then continue at 100 to 125 mL/kg/day (1½–2 times maintenance rate)

Furosemide (2–4 mg/kg every 8–12 hours IV, SC, or PO)

Note: Only use after patient is fully rehydrated.

Prednisone (1–2 mg/kg q12–24 h PO)

Note: Only use after diagnosis obtained (see text).

Pamidronate (1.0–2.0 mg/kg diluted in 250 mL of NaCl IV over 2 hours every 2–4 weeks)

Zoledronate (0.1–0.25 mg/kg diluted in 60 mL of NaCl IV over 15 minutes every 2–4 weeks)

HM Management

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HM Management





Bisphosphonates

- Zoledronate most commonly used
 - 0.1mg/kg IV over 15-20 minutes, no more than 4mg/dog
 - Monthly treatments
 - Monitor renal values
 - Bisphosphonate-related osteonecrosis of the jaw (BRONJ) - typically associated with chronic dosing
- Pamidronate less commonly used
 - Zoledronate more potent

Poll Question #2

Hypercalcemia is most commonly associated with which subtype of lymphoma?

- A. B-cell lymphoma
- B. Indolent lymphoma
- C. Renal lymphoma
- D. T-cell lymphoma

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Hypercalcemia is most commonly associated with which subtype of lymphoma?

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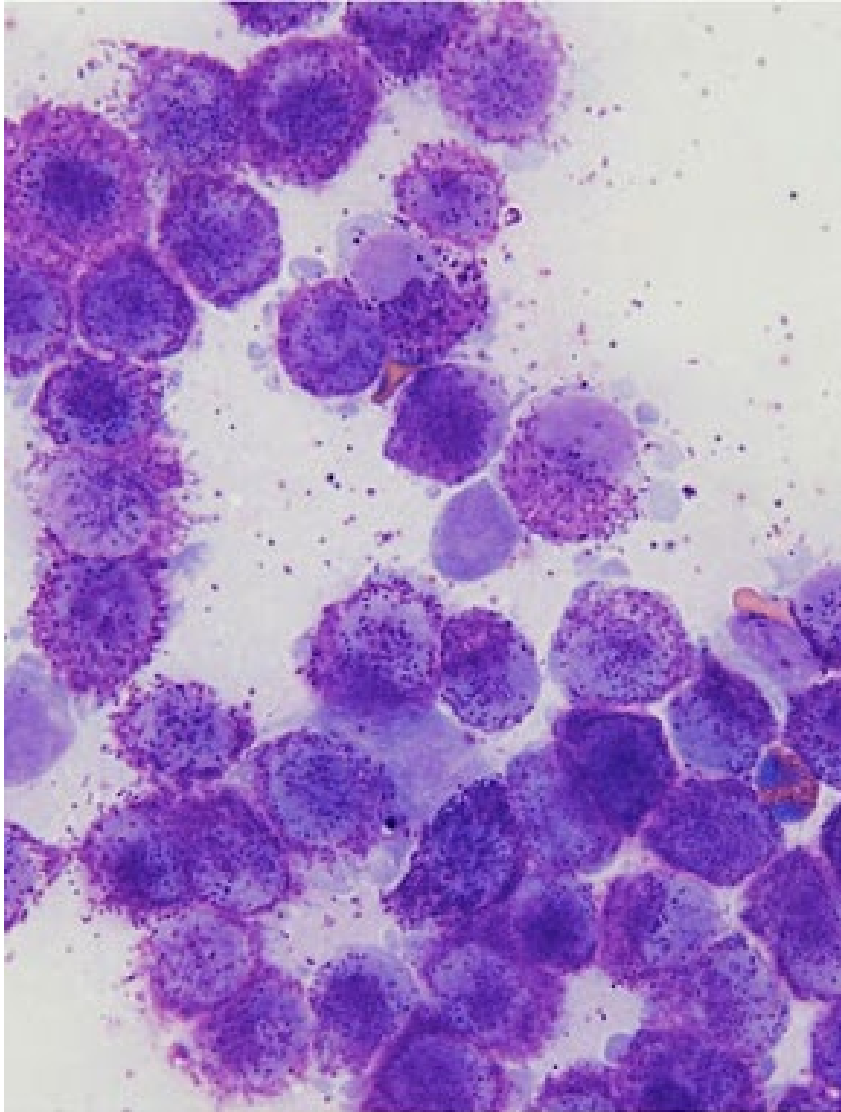
~~C. Renal lymphoma~~

D. T-cell lymphoma

Anemia & Thrombocytopenia

Anemia

- Likely one of the most common paraneoplastic syndromes in cancer patients
- Paraneoplastic anemia caused by same major pathogenic mechanisms as other causes of anemia
 - Blood Loss
 - Decreased RBC production
 - Increased RBC destruction

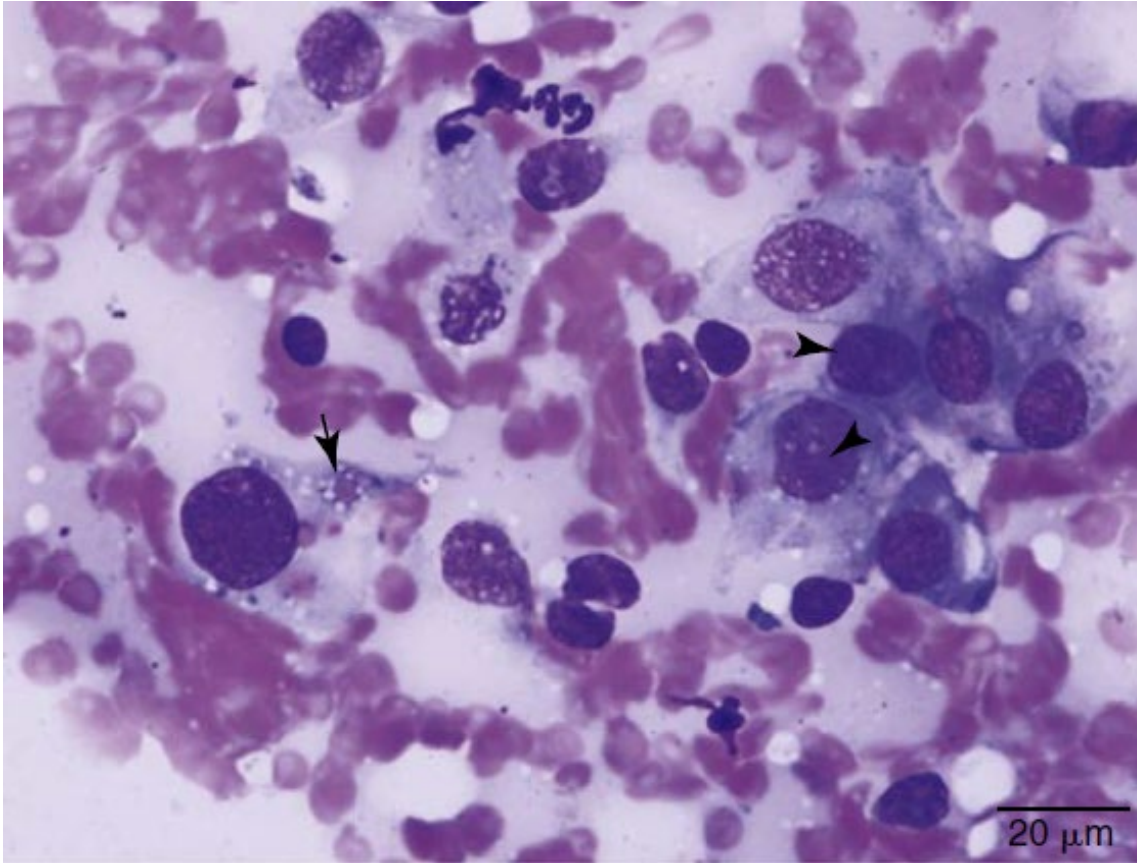


Anemia – Blood Loss

- Acute hemorrhage: hemangiosarcoma, other splenic tumors, adrenal tumors, thyroid carcinoma
- Chronic, low-grade hemorrhage: GI tumors, nasal tumors, urinary tract tumors
 - Also tumors that cause GI ulceration
 - Mast Cell Tumors
 - Gastrinoma

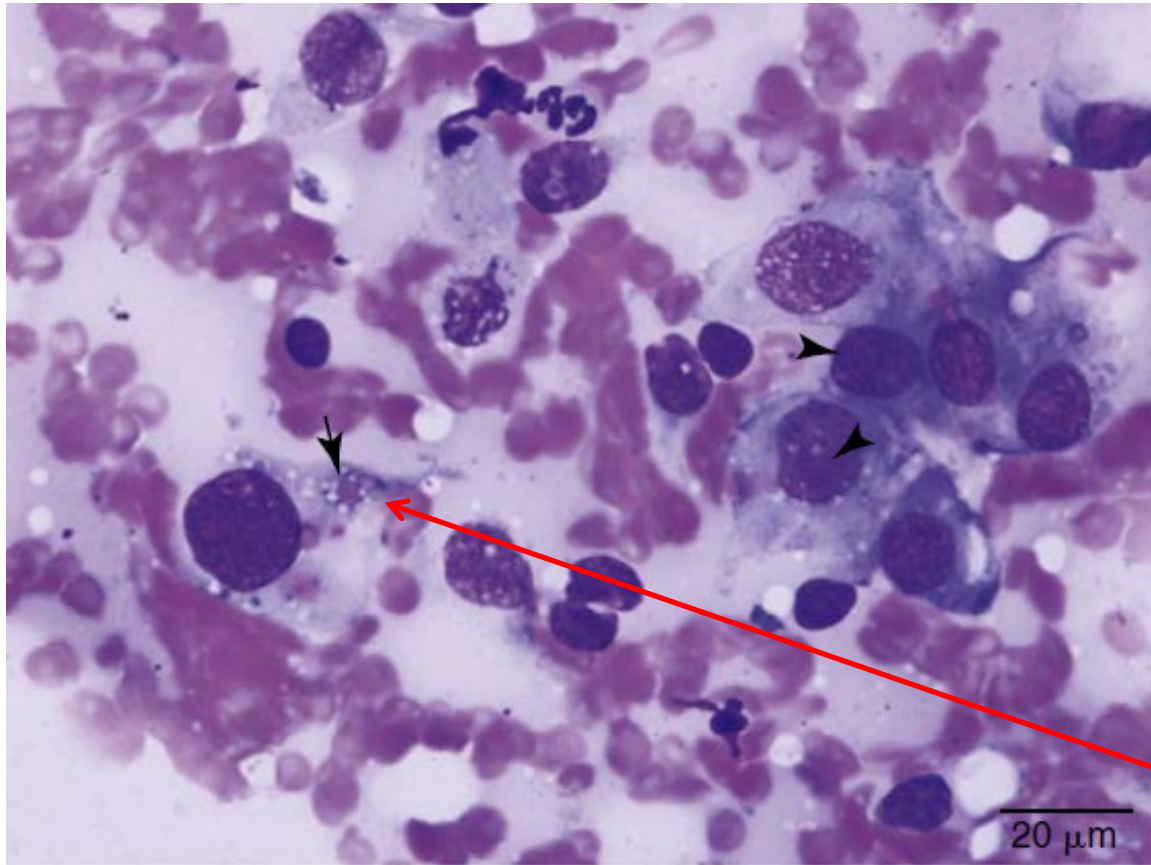
Anemia – Increased RBC Destruction

- Immune mediated hemolytic anemia – most commonly lymphoma and leukemia, FeLV in cats
 - 30-40% of dogs with LSA and 40-58% of cats with LSA
- Non-immune mediate hemolytic anemia
 - Microangiopathic hemolytic anemia (MAHA) - hemangiosarcoma
 - Tumor cell erythrophagocytosis – histiocytic sarcoma
 - Oxidative damage - lymphoma



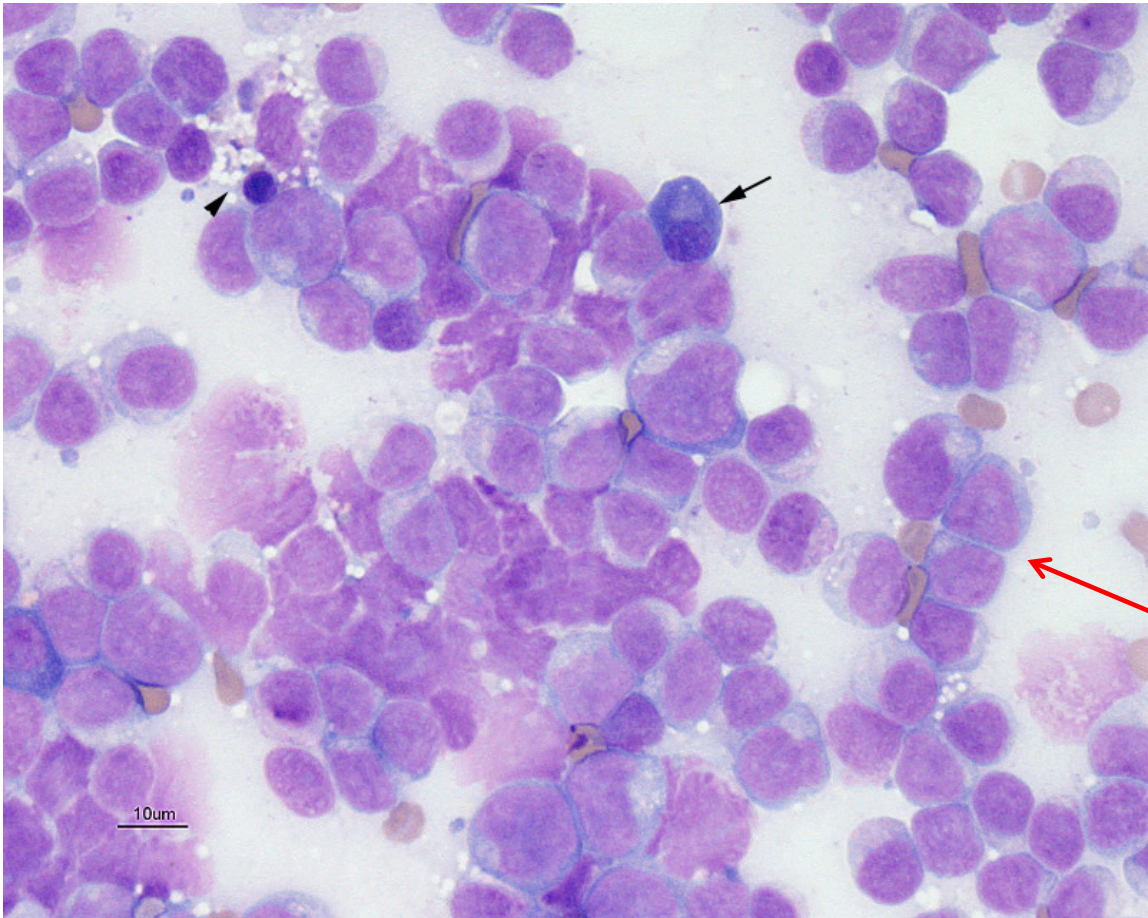
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Anemia – Decreased RBC production

- Anemia of chronic disease
 - Nonregenerative, normocytic, normochromic
- Myelophthysis – replacement of normal bone marrow with abnormal tissue
 - Most common = hematopoietic cancers – leukemia, lymphoma, multiple myeloma, mast cell, histiocytic sarcoma
- Aplastic anemia secondary to paraneoplastic hyperestrogenism



Hyperestrogenism

- Most commonly associated with Sertoli cell tumors, ~50% of which occur in cryptorchid testes
- Clinical signs
 - Bilaterally symmetric alopecia, cutaneous hyperpigmentation, epidermal thinning
 - Gynecomastia
 - Penile atrophy, prostatic atrophy
- Aplastic anemia

Poll Question #3

Paraneoplastic IMHA is most commonly caused by

- A. Lymphoma
- B. Hemangiosarcoma
- C. Histiocytic Sarcoma
- D. Mast Cell Tumors

Poll Question #3

Paraneoplastic IMHA is most commonly caused by

A. Lymphoma

~~B. Hemangiosarcoma~~

~~C. Histiocytic Sarcoma~~

~~D. Mast Cell Tumors~~

Thrombocytopenia

- Dogs – 13-36% of dogs with cancer present with thrombocytopenia
- Cats – 39% of thrombocytopenic cats diagnosed with cancer
- Mechanisms:
 - Decreased platelet production
 - Increased platelet destruction
 - Increased platelet sequestration
 - Increased platelet consumption

Paraneoplastic Thrombocytopenia

- Decreased production – myelophthisis and hyperestrogenism
- Immune-mediated – lymphoma, multiple myeloma, histiocytic sarcoma
- Non-immune-mediated destruction – microangiopathy (hemangiosarcoma)
- Platelet sequestration, usually in spleen – splenic lymphoma, feline MCT, hemangiosarcoma
- Consumption – acute hemorrhage, hypercoagulability (common in cancer patients)

Hypertrophic osteopathy (HO)



HO

- Generalized osteoproliferative disorder of periosteum
- Affects long bones, usually starts distally and progresses proximally
- Presentation: swelling and/or edema of limbs, pain, difficulty walking, limbs warm to the touch
 - Concurrent bilateral serous to mucopurulent ocular discharge and episcleral injection



HO Causes & Pathogenesis

HO Causes & Pathogenesis

- Neoplastic
 - Usually metastatic neoplasia, most commonly osteosarcoma
 - TCC, HCC, others
 - Pulmonary masses – carcinoma, histiocytic sarcoma
- Non-neoplastic
 - Infectious/inflammatory lung disease
 - Heart worm infection
 - Bacterial endocarditis
 - Esophageal granulomas or foreign bodies
 - Congenital megaesophagus
- Cats – idiopathic, primary lung tumors

HO Treatment

- Remove underlying cancer
 - Usually challenging because HO most commonly seen with metastatic nodules
 - Metastatectomy if only a few lesions
 - Lameness resolution often quickly (24-48 hours)¹
 - Chemotherapy if responsive tumor type
 - Limited case reports
- Palliative care
 - Multimodal pain control – NSAIDs, gabapentin, opioid, amantadine
 - Bisphosphonates – not evaluated in dogs for treatment of HO
 - Humane euthanasia

1. Liptak JM, Monnet E, Dernell WS, et al.: Pulmonary metastatectomy in the management of four dogs with hypertrophic osteopathy, *Vet Comp Oncol* 2:1–12, 2004.

Paraneoplastic Hypoglycemia

- Insulinoma (pancreatic beta-cell tumors)
 - Diagnosis – hypoglycemia (<60mg/dL) + paired normal or elevated insulin levels
 - Medical management
 - Prednisone 0.25mg/kg PO BID starting dose, slow increase if hypoglycemia not controlled
 - Small, frequent feedings
- Non-islet cell tumors
 - Primary liver tumors – hepatocellular carcinoma or adenomas
 - Smooth muscle tumors – leiomyosarcoma

Poll Question #4

Hypertrophic osteopathy can be caused by what non-neoplastic disease?

- A. Heartworm infection
- B. Bacterial endocarditis
- C. Esophageal granulomas
- D. All of the above

Poll Question #4

Hypertrophic osteopathy can be caused by what non-neoplastic disease?

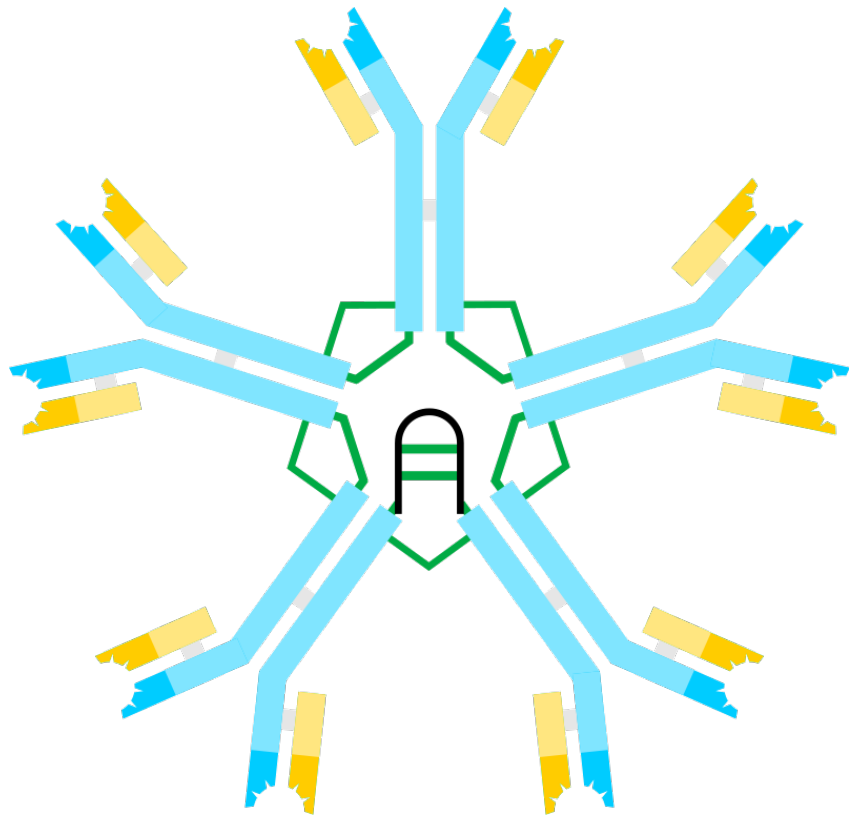
- A. Heartworm infection
- B. Bacterial endocarditis
- C. Esophageal granulomas
- D. All of the above

Fever

- True incidence unknown, some studies suggest <10% of dogs presenting with fever have cancer
- Most frequently associated with hematopoietic cancers
- Innate immune response against tumor antigens
- Oncology patients with fevers – important to assess for infection
 - Necrotic tumors
 - GI ulceration
 - Sepsis secondary to leukopenia (cancer vs. chemotherapy)

Erythrocytosis

- Renal tumors most commonly
 - Others – nasal fibrosarcoma, cecal leiomyosarcoma
- Paraneoplastic erythrocytosis associated with increased erythropoietin (EPO)
 - Usually produced by tumor cells
- Usually resolves with removal of primary tumor
- Complication: hyperviscosity syndrome



Hyperviscosity Syndrome

- Constellation of clinical signs resulting from increased blood viscosity
 - Neurologic: abnormal mentation, ataxia, seizures
 - Ocular: enlarged and tortuous retinal vessels, retinal hemorrhages, retinal detachment
 - Cardiac: hypertrophic cardiomyopathy and congestive heart failure
- Causes
 - Multiple myeloma – usually IgM macroglobulinemia
 - Polycythemia vera
 - Paraneoplastic erythrocytosis
- Emergent therapy: plasmapheresis or phlebotomy + IVF

Myasthenia Gravis

- Paraneoplastic most commonly associated with thymoma
 - Thymomas associated with numerous other immune-mediated diseases
 - Removal of thymoma and/or radiation therapy – not consistent responses
- Others = osteosarcoma, oral sarcoma, cutaneous lymphoma
- Same pathogenesis – antibodies formed against nicotinic acetylcholine receptors
 - Definitive diagnosis = presence of circulating antibodies against ACh receptors

Poll Question #5

Paraneoplastic erythrocytosis is most commonly associated with cancers affecting which location?

- A. Liver
- B. Kidney
- C. Heart
- D. Spleen

Poll Question #5

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Questions?

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