

Hematopoietic neoplasia

Is there more than lymphoma?

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What's out there?

Cellular origin

➤ Myeloid/Non-lymphoid

- Erythrocytes
- Granulocytes
- Thrombocytes
- Mast cells
- Histiocytes / Monocytes / Macrophages

➤ Lymphoid

- Lymphocytes
- Plasma cells

Disease presentation

➤ Leukemia

- Acute/poorly differentiated
- Chronic/well differentiated

➤ Mass-lesion ("solid tumor")

- Lymphoma
- Mast cell tumor
- Plasmacytoma
- Histiocytic sarcoma

• Often both presentations exist

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So, what's out there?

Erythrocytes

- Erythroblastic leukemia
- Polycythemia vera (PCV)

Granulocytes

- Acute myeloid leukemia (AML)
- Chronic myeloid leukemia (CML)
- Myelodysplastic syndrome
- Hypereosinophilic syndrome

Thrombocytes

- Megakaryoblastic leukemia
- Essential thrombocytosis

Lymphocytes

- Acute lymphoblastic leukemia (ALL)
- Chronic lymphocytic leukemia (CLL)
- non-Hodgkin lymphoma
- Hogkin-like lymphoma

Plasma cells

- Plasma cell leukemia
- Extrasseous plasmacytoma (cutaneous, mucosal)
- Solitary osseous plasmacytoma
- Multiple myeloma

Mast cells

- Mast cell leukemia
- Mast cell tumor ((sub)cutaneous, mucosal, visceral)

Histiocytes/Macrophages

- Dendritic cell leukemia
- Histiocytoma
- Langerhans cell histiocytosis (cutaneous, pulmonary)
- Reactive histiocytosis (cutaneous, systemic)
- Histiocytic sarcoma (localized, disseminated)
- Hemophagocytic syndrome
- Progressive histiocytosis (C)

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Ekita

Border collie FN gY

- Presented for post-operative RTx following incomplete resection STS distal LF limb
- No signs, normal pre-anesthetic exam

	160614	Reference
Hematocrit	0.44	0.42 – 0.61
WBC	59.9	4.5 – 14.6
Neutrophils	4.8	2.9 – 11.0
Lymphocytes	54.5	0.8 – 4.7
Monocytes	0.6	0.0 – 0.9
Thrombocytes	287	144 – 603

Ddx: hypoadrenocorticism, thymoma, post-vaccination young animals, chronic antigenic stimulation (inflammatory disorders, infections) (cat: stress, hyperthyroidism)

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Ekita

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Ekita

CD8+ T cell leukemia (CLL)

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Canine CLL

- Mostly asymptomatic
 - incidental finding in older animal
 - seen for "wellness" exam or pre-anesthetic screen
- if symptomatic: nonspecific signs
 - lethargy, reduced appetite, weight loss
- P.E: peripheral and visceral lymphadenopathy, splenomegaly
- Leukocytosis due to lymphocytosis
 - lymphocytes: $15 - 1.600 \times 10^9/L$ (RR: $0.8 - 4,7 \times 10^9/L$)
- Mild anemia (>30%), mild thrombocytopenia
- Bone marrow: >30% small mature lymphocytes
- Occasionally monoclonal gammopathy
- Immunophenotype
 - 70-75% CD8+ T cell
 - rest: CD4+ T cell, B-cell

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Follow-up Ekitu

Treatment

- First-line protocol: Chlorambucil + Prednisolone
- Rescue protocols: CCNU; high-dose COP/CHOP
- Role for splenectomy?

	D0	D11	D42	D783	Reference
Hematocrit	0.44	0.42	0.40	0.43	0.42 – 0.61
WBC	59.9	21.8	12.6	13.6	4.5 – 14.6
Neutrophils	4.8	17.7	11.1	11.7	2.9 – 11.0
Lymphocytes	54.5	2.8	0.6	1.6	0.8 – 4.7
Monocytes	0.6	1.3	0.7	0.1	0.0 – 0.9
Thrombocytes	287	383	366	467	144 - 603

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Canine CLL

Prognosis

Atypical CLL 22d

B-CLL 480d

T-CLL 930d

survival probability

Time (days)

Comazzi et al, 2012

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Acute leukemia

Presence of blasts in peripheral blood and/or bone marrow

Mostly lymphoid

- in cats also erythroid leukemia (FeLV+)

Compared to CLL, typically

- more ill
- more severe bone marrow suppression (neutropenia, thrombocytopenia)
- poor prognosis

Challenge: ALL vs. stage V lymphoma

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Indy

Cocker spaniel

MN 10Y

Problem: less active since 2-weeks

History:

- No other signs, but some muscle atrophy
- NSAID's gave temporary improvement

Clinical examination

Unremarkable, other than for mild muscle atrophy

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Indy

Hematology

- Moderate, non regenerative anemia (Ht 19%)
- Normal leukogram, normal thrombocyte count

Clinical Chemistry	Result	Reference range units
Urea	8.5	3.0-12.5 mmol/L
Creatinine	114	50 - 129 µmol/L
ALP/ALP ⁹⁵	252 / 376	<89 IU/L
ALAT	39	<70 IU/L
Bile acids	2	<10 µmol/L
Glucose	5.3	4.2 - 5.8 mmol/L
Total calcium	3.65	1.98 - 2.97 mmol/L
Total protein (hep)	118	55-72 g/L
Albumin (hep)	16	26-37 g/L

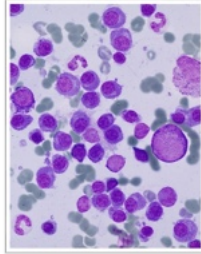
Urinalysis

- s.g. = 1.019, pH 6, Glucose/Ketones/Bilirubin/Hb all negative
- UPC = 4.2; no active sediment

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Indy

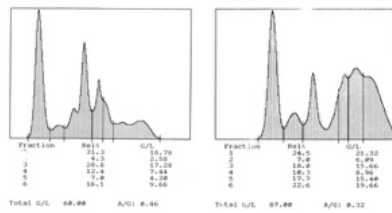
Protein spectrum (serum)	Patient	Reference range
Total protein	115	55-72 g/L
Albumin	15	26-37 g/L
Alpha 1	1.7	5-10 g/L
Alpha 2	9.2	4-13 g/L
Beta 1	3.2	3-10 g/L
Beta 2	67.9	4-10 g/L
Gamma	17.9	3-9 g/L



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PROTEIN DIAGNOSTICS

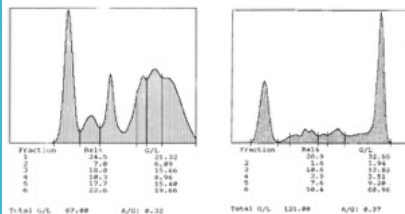
acute vs chronic inflammation



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PROTEIN DIAGNOSTICS

polyclonal vs monoclonal gammopathy



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Plasma cell neoplasms

- Localized forms
 - Plasmacytoma: skin, oral cavity, stomach, rectum
 - Cutaneous plasmacytosis
 - Solitary extra-osseous plasmacytoma
 - Solitary osseous plasmacytoma (SOP)
- Systemic forms (multiple myeloma)
 - Monoclonal expansion of plasma cells
 - Dog: 8% of all hematopoietic neoplasias; Cat: rare
 - Middle-aged to older animals (8-9 Y)
 - Etiology: unknown (chronic antigenic stimulation?)
 - Monoclonal gammopathy
 - IgG = IgA
 - occasionally biclonal, "non-secretory" or IgM (Waldenström's macroglobulinemia)

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Solitary plasma cell tumors



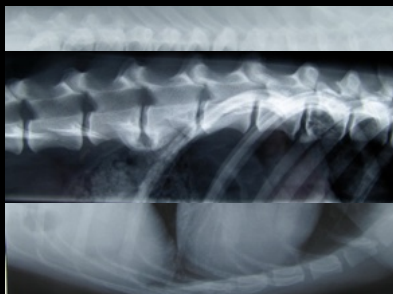
Mucocutaneous PCT

Rectal PCT

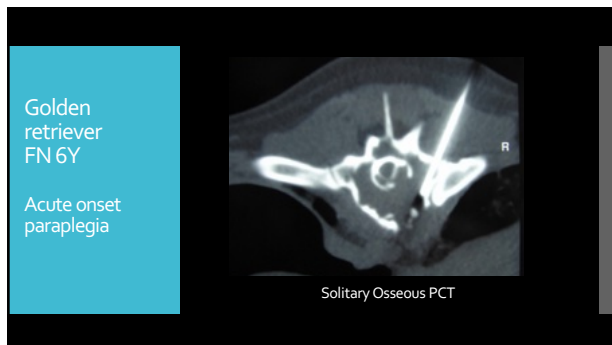
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Golden retriever
FN 6Y

Acute onset
paraplegia



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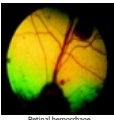
Multiple
myeloma

Signs

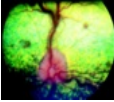
- Often non-specific
- Infiltration into organs/bone marrow
- Paraproteinemia

Associated conditions

- Hemorrhagic diathesis; due to thrombocytopenia, thrombocytopathy, hyperviscosity, hypertension
- Hyperviscosity syndrome
 - IgA dimerization, IgM
- CNS, cardiac, ocular signs
- Hypercalcemia ($\pm 20\%$)
- Osteolytic lesions
- Infections (opportunistic)
- Renal disease

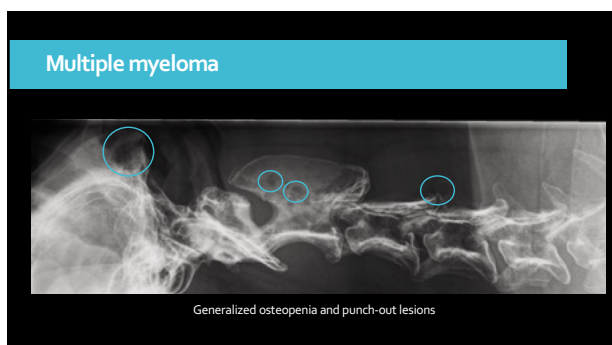


Retinal hemorrhage



Venous dilatation with
tortuous vessels

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Multiple myeloma

diagnosis

Myeloma is a syndrome, multiple diagnostic criteria needed

Bence-Jones proteinuria
(exclude infectious diseases)

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Multiple myeloma

therapy

Treatment

- Melphalan: 10 days 0.1 mg/kg 1dd PO, then 0.05 mg/kg 1dd PO
- Prednisolone: 1 mg/kg 1dd, if in CR gradually taper and stop

Prognosis (mOSI)

- Prednisolone 220 days
- Prednisolone + Melphalan 540 days
- Most dogs die from disease-related problems

Prognostic factors

- Negative: hypercalcemia, Bence Jones proteinuria, extensive osteolytic lesions, (no response to chemotherapy)
- No effect: sex, Ig-subclass, hyperviscosity, azotemia

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Feline plasma cell neoplasia

Two types of clinical presentation:

- (sub)Cutaneous form
 - Focal, multifocal, diffuse (cutaneous plasmacytosis)
 - Alopecia, redness, scaling
 - Head & Neck, Limbs
 - Systemic clinical signs are rare
 - Tx: surgical excision, chemotherapy
 - survival 1.080 days (30–1.680)

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Feline myeloma

Lecot et al., 2024

2. *Visceral and/or bone marrow form*

- Older (median 12Y) DSH, M > F
- Non-specific signs: lethargy, anorexia, weight loss

Clinical pathology

- 100% hyperglobulinemia (± 100 g/L); monoclonal (95%), biclonal (5%)
- $\pm 60\%$ mild anemia, proteinuria
- $\pm 50\%$ hypoalbuminemia, azotemia
- $\pm 33\%$ hyperviscosity
- $\pm 15\%$ ionized hypercalcemia

Imaging

- most commonly affected spleen > liver > bone marrow
- 30-50% (multi)focal osteolysis, mostly vertebrae and pelvis

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Feline multiple myeloma

Lecot et al., 2024, Cannon et al., 2015

Therapy

- ORR prednisolone + melphalan / cyclophosphamide / chlorambucil 87, 90, and 100% respectively.
- cyclophosphamide less toxic than melphalan (23 vs 65%)

Prognosis

- mOST: 122 days (0 – 1.403)

	Melphalan	Cyclophosphamide
Overall response	5/8 (2 CR, 3 PR)	5/6 (3 CR, 2 PR)
Tx discontinued due to Gr3-4 toxicity	5/8	0/5
mOST (d)	252	394

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Tommie

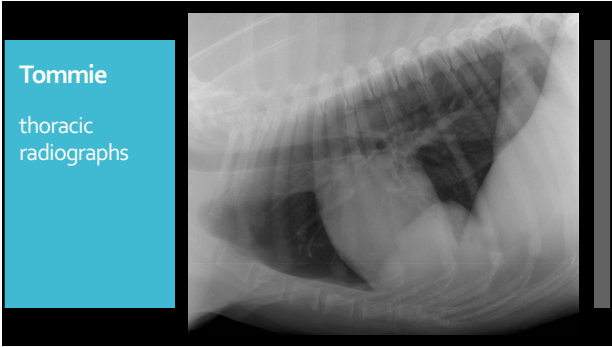
Bernese Mountain dog MN 6Y

- History: for 2 days lethargy, reduced appetite
- Medical history: histiocytoma, travelled to Southern France & Italy
- General physical examination:
 - Respiratory: panting, no stertor/stridor
 - Pulse: 132/min, strong bilateral femoral pulses
 - Rectal temperature: 39.2°C
 - Mucous membranes: pale oral MM, no jaundice
 - Peripheral lymph nodes: not enlarged
 - Abdominal palpation: mildly enlarged spleen

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Tommie					
Hematology	Tommie	Ref. Range	Chemistry	Tommie	Ref. Range
Hematocrit	0.20	0.42 – 0.61 L/L	Urea	4.4	141 – 150 mmol/L
Reticulocytes	8.2%	< 2%	Creatinine	80	50 – 129 µmol/L
Leukocytes	13.0	4.5 – 14.6.10 ⁹ /L	Sodium	145	141 – 150 mmol/L
Differentiation	Normal		Potassium	4.1	3.6 – 5.6 mmol/L
Blood parasites	Not observed		Calcium	2.53	1.98 – 2.97 mmol/L
Trombocytes	67	144 – 603.10 ⁹ /L	ALP	178	< 89 U/L
Coagulation panel					
PT	7.6s	7.2 – 9.9 s	ALAT	100	< 70 U/L
APTT	15.3s	13.2 – 18.2 s	Bile acids	7	<10 µmol/L
Fibrinogen	2.5 g/L	1.0 – 2.7 g/L	Total protein	62	55 – 72 g/L
Coombs' test	Negative		Albumin	28	26 – 37 g/L

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What are histiocytes?

Antigen-presenting cells and part of the immune system
Express β -2 integrins: hetero-dimer consisting of an α - (CD11b-d) and a β 2-subunit (CD18)

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How do we recognize these cells?

- CD38 commonly used, but nonspecific
 - expressed on all leukocytes incl. all histiocytic cells
 - only useful in a panel (to exclude other round cell tumors)
- IBA1 specific for histiocytic cells, but nondiscriminatory between histiocytic/macrophage derived diseases
 - 100% in canine and feline **inflammatory, reactive and neoplastic** histiocytic diseases
 - 100% in round cell tumors incl melanomas, lymphomas, mast cell tumors, plasmacytomas

Pierrezan 2014

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What is out there?

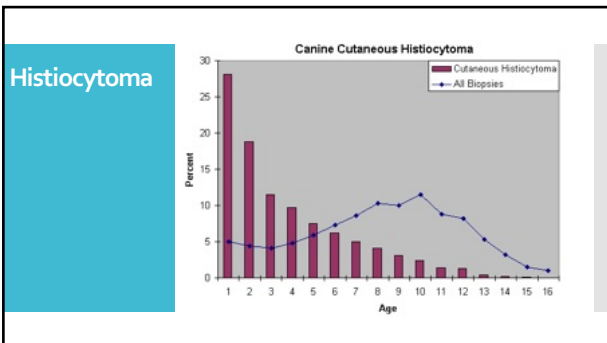
Cell type	Dog		Cat
	Localized	Systemic	
Langerhans cell (CD11c ⁺) Cadherin ⁺	Histiocytoma	Langerhans cell histiocytosis	Feline pulmonary Langerhans cell histiocytosis
Interstitial dendritic cell (CD11c ⁺) Cadherin ⁺	Cutaneous histiocytosis	Systemic histiocytosis	-
	Histiocytic sarcoma (peri)articular, ocular, Pulmonary, CNS	Disseminated HS (malignant histiocytosis) Dendritic cell leukemia	Feline progressive histiocytosis, Histiocytic sarcoma
Macrophage (CD11d ⁺)	-	Hemophagocytic syndrome	Hemophagocytic syndrome

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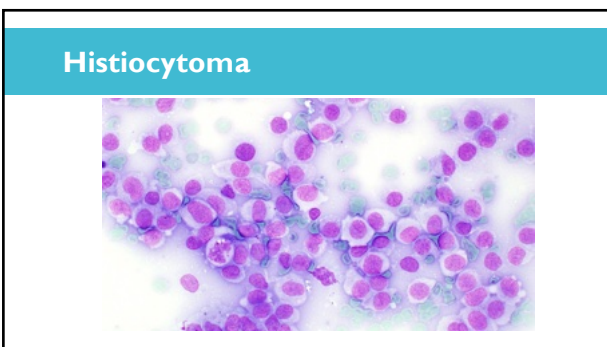
Histiocytoma



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Histiocytoma

Therapy

- Wait-and-see (especially in younger dogs)
- No steroids!
- Extreme or persistent cases
 - Surgery (incl. cryo-/electrosurgery)
 - Electrochemotherapy

Excellent prognosis!!

- typically undergo spontaneous regression
- recurrence rate after surgery extremely low
- development of histiocytoma at new site is rare

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Histiocytoma
self-cure

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Histiocytic sarcoma

Multiple anatomical/clinical presentations

- Localized HS
 - Subcutaneous HS
 - Splenic HS
 - Periarticular HS
 - CNS HS
 - Ocular HS
- Disseminated HS (a.k.a malignant histiocytosis)
- Leukemia

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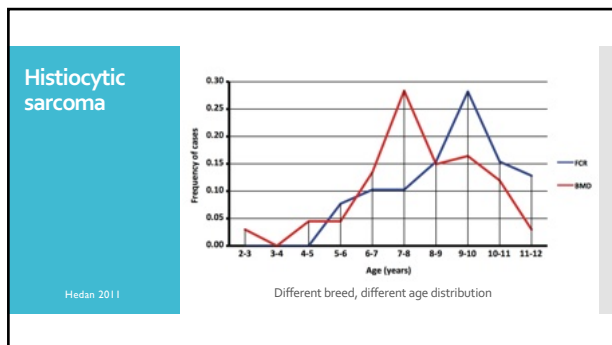
Histiocytic sarcoma

Dog breeds

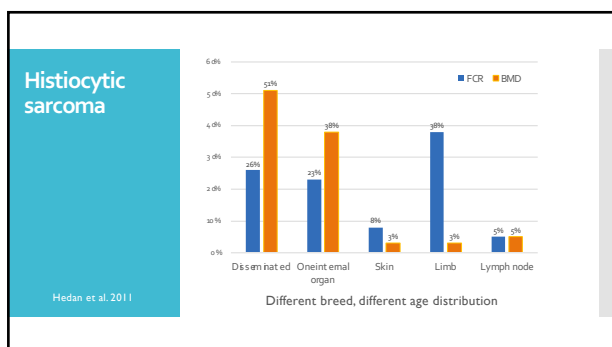
- Bernese mountain dog
- Flatcoated retriever
- Rottweiler
- Golden retriever
- Labrador retriever
- Welsh Corgi Pembroke (Japan)
- miniature Schnauzer (UK)

Cats??

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Cause HS?

Genetic factor

- Breed predilection- different breeds in various countries:
 - Worldwide: Bernese mountain dog, Flatcoated retriever, Golden retriever, rottweiler
 - Japan: Welsh corgi
 - UK: miniature Schnauzer
- Familial occurrence
- Polygenic
- Heritability 0.30

“Environmental” factor

- Chronic joint disease ≈ periarticular HS
 - Microtrauma leading to malignant transformation of dendritic cells in a chronically inflamed synovium??

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Clinical Signs

- Typically non-specific
 - Anorexia (92%)
 - Lethargy/weakness (90%)
 - Weight loss (88%)
- Sometimes:
 - Fever/Hyperthermia (43%)
 - Abnormal pulmonary auscultation (31%)
 - Coughing (19%)
 - Abnormal cardiac auscultation (16%)

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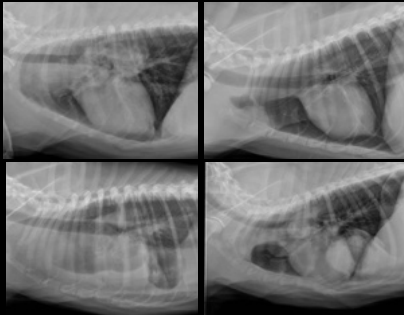
Clinical pathology

- Often: anemia, thrombocytopenia
 - Most commonly regenerative, Coombs' negative
- Frequent: neutrophilia, monocytosis, lymphopenia
 - Leukemia extremely rare
- Sometimes:
 - increased liver enzymes (AF/ALAT),
 - Hypercalcemia
- Hyperferritinemia
 - Non-specific
 - Following exclusion IMHA, HS most common cause

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Diagnostic Imaging

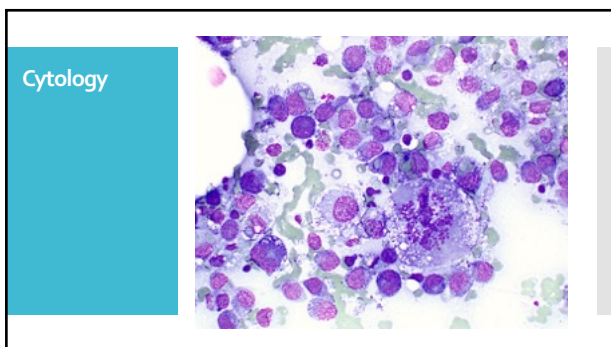
thorax



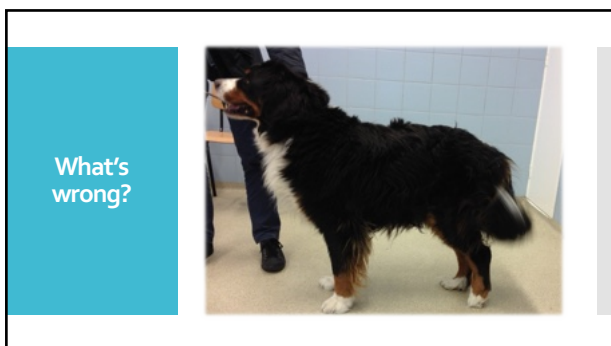
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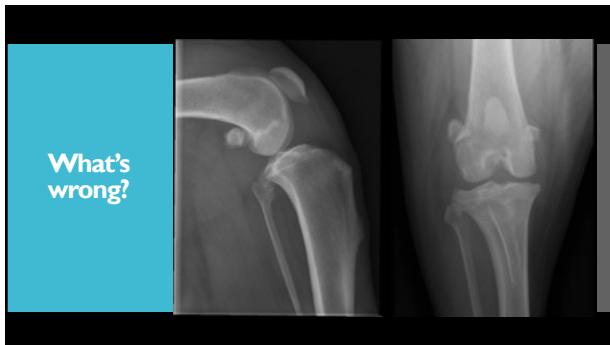
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Periarticular HS

- Most common synovial tumor
- Most common: stifle, elbow
- ±50% Rottweilers

Signs

- Lameness, joint swelling,
- Often ruptured CCL
- Often systemic spread

Diagnosis

- Rx: aggressive polyostotic, osteolytic bone lesion
- typically with soft tissue mass



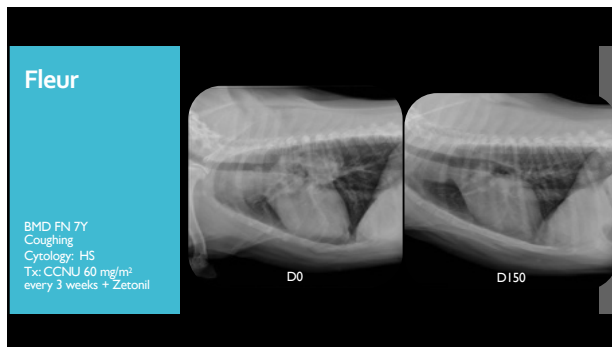
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Treatment options

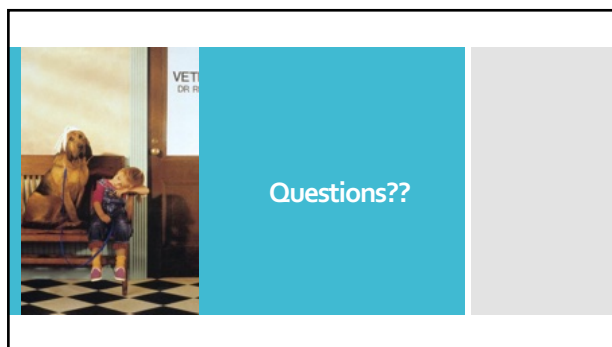
1. Surgery: amputation, splenectomy, enucleation
1. Radiotherapy: palliative or curative intent
2. Chemotherapy
 - CCNU (59 dogs): ORR 46%, MST 106d
 - CCNU + Doxo-/Epirubicine
3. Combinations of the above
 - Localized forms Sx ± RTx + CTx: 2 LR, 8 Mets,
 - OST 568d
4. Liposomal clodronate

Skorupski et al. JNM 2007
Skorupski et al. VCO 2009

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