



*Ferret Lymphoma:  
A retrospective review of disease,  
diagnostics, and treatment*

Natalie Antinoff, DVM, ABVP (Avian)

Martha Needham, DVM

Gulf Coast Veterinary Specialists

Houston, TX

## *Fact or Fiction?*

- Most ferrets with lymphoma have big peripheral lymph nodes
- Ferrets with lymphoma commonly have high lymphocyte counts
- There is a “better” protocol to treat lymphoma

## *Fact or Fiction?*

- Young ferrets with lymphoma get a worse form with a worse prognosis and shorter life expectancy
- Older ferrets get a chronic form that doesn't respond well to treatment
- Ferrets with lymphocytic leukemia (bone marrow) have the worst prognosis

# *Ferret Lymphoma*

## *Case Study: "Randy"*

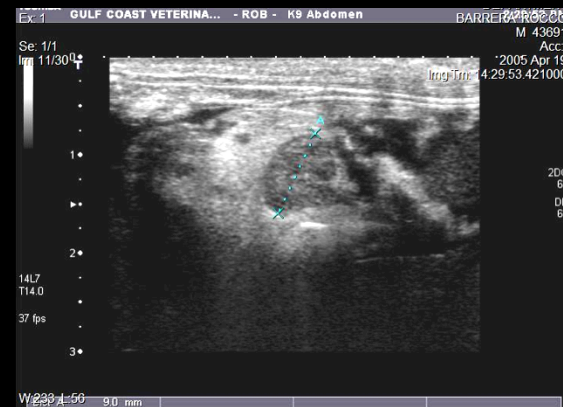
- 9/15/99
- 7 yr MC
- Hair Loss
- PE
  - BARH,
  - Peripheral lymphadenopathy
  - adrenomegaly



# *Ferret Lymphoma*

## *Case Study: "Randy"*

- US: Splenic infiltrate, mesenteric lymphadenopathy
- Aspirate: Lymphosarcoma
- CBC: WBCs 23,000, lymph 19,278



# *Ferret Lymphoma*

## *Case: "Randy"*

- 11/12/99 (2 months later)
  - peripheral lymphadenopathy
  - Splenomegaly
  - abdominal masses
  - arrhythmia
- Thoracic Radiographs: nodules cranial to heart
- Bone Marrow: erythroid hypoplasia, lymphocytosis
- CBC: WBCs 38,000, lymph 32,555



# *Ferret Lymphoma* *Case Study: "Randy"*



# *Ferret Lymphoma*

## *Case Study: "Randy"*

- Lymphoma
  - Stage 4
  - Multicentric
  - Leukemic
- 11/17/99
  - Aggressive Chemotherapy
  - 12/28/99 WBC 31,900
- 1/4/00
  - Radiation Therapy
  - 1/18/00 WBC 8,000





# *Ferret Lymphoma Case Study: "Randy"*

- Prior to RT



# *Ferret Lymphoma Case Study: "Randy"*

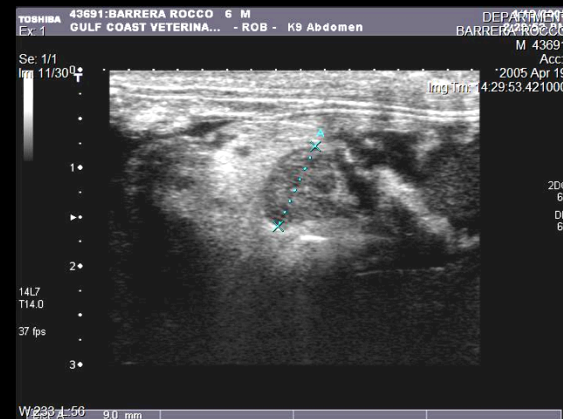
- 6 weeks of RT



# *Ferret Lymphoma*

## *Case Study: "Randy"*

- US: Splenic infiltrate, mesenteric lymphadenopathy
- Aspirate: Lymphosarcoma



# *Ferret Lymphoma*

## *Case Study: “Randy”*

- Maintained on Cytoxan & Vincristine
- 10/12/00 (11 months after initiating treatment)
  - US: infiltrated spleen, cystic kidneys, mesenteric lymphadenopathy – large single mass
  - Radiation + Adriamycin
- 3/17/01 (15 months)
  - Dyspneic, minimally responsive
  - Euthanized
- Survival Time: 15 months

# *Ferret Lymphoma*

- Lymphoma
  - Review
- Lymphoma in Ferrets
  - Descriptive Literature
  - Treatment Literature
- Retrospective Study at Gulf Coast
  - Diagnostics
  - Descriptive
  - Treatment
  - Preliminary Data



# *Review*

# *Ferret Neoplasia*

- Estimated up to 100%
  - (Carpenter et al 1981)
- Neoplasia (Li et al, 1998)  
(n = 574)
  - Pancreatic Islet Cell      21.7%
  - Adrenocortical Cell      16.7%
  - Lymphoma                      11.9%

# *Lymphoma*

- Lymphoma vs. Lymphosarcoma
- other Neoplasia
  - sarcoma: malignancy
  - oma: benign process
- Lymphocytic Leukemia
  - Leukemia: peripheral blood



# *Classification*



- Staging
  - Clinical location and extent
- Grading
  - Characteristics of the cells
- Phenotyping
  - Origin of cells

# Staging

- Clinical description of the disease
  - location of the neoplasia
  - extent of dissemination
  - World Health Organization (WHO)
    - generally accepted by the American College of Veterinary Pathologists (ACVP).
  - clinical presentation, anatomic location, and disease progression

# *Ferret Lymphoma*

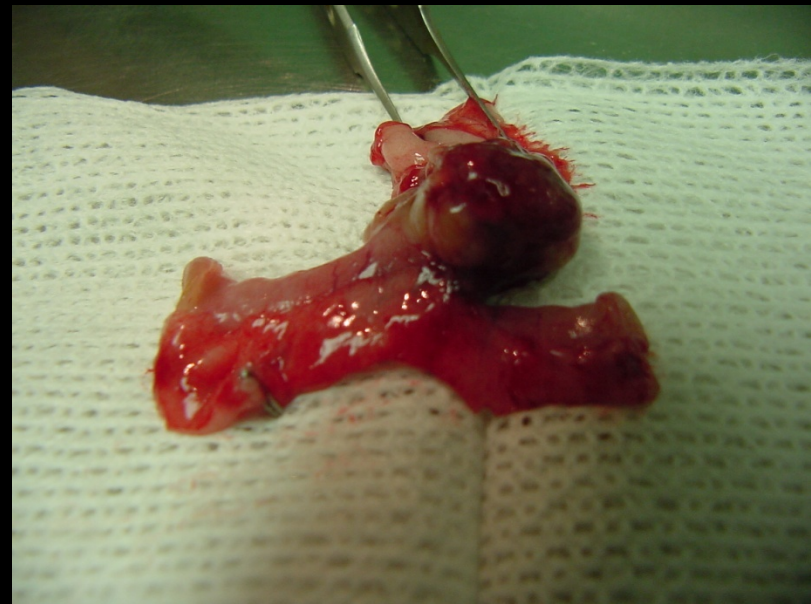
## *Staging : Canine/Human*

Stage	Characteristics
I	Affecting a single node or tissue in a single organ
II	Multiple lymph nodes in one area of the body (same side of the diaphragm)
III	Generalized lymph node involvement (both sides of the diaphragm)
IV	Any of the above + liver or spleen
V	Any of above + blood or bone marrow

# *Ferret Lymphoma*

## *Staging : Feline*

- Mediastinal Lymphomas
  - mediastinal mass +/- pleural effusion
- Alimentary lymphoma
  - stomach, intestine, or mesenteric LN
- Peripheral LNs
  - single/multiple PLNs
- Multicentric
  - multiple sites, bone marrow, extranodal
- Extranodal
  - Eye, kidney, CNS, heart



- Lymphocytic leukemia
  - bone marrow involvement

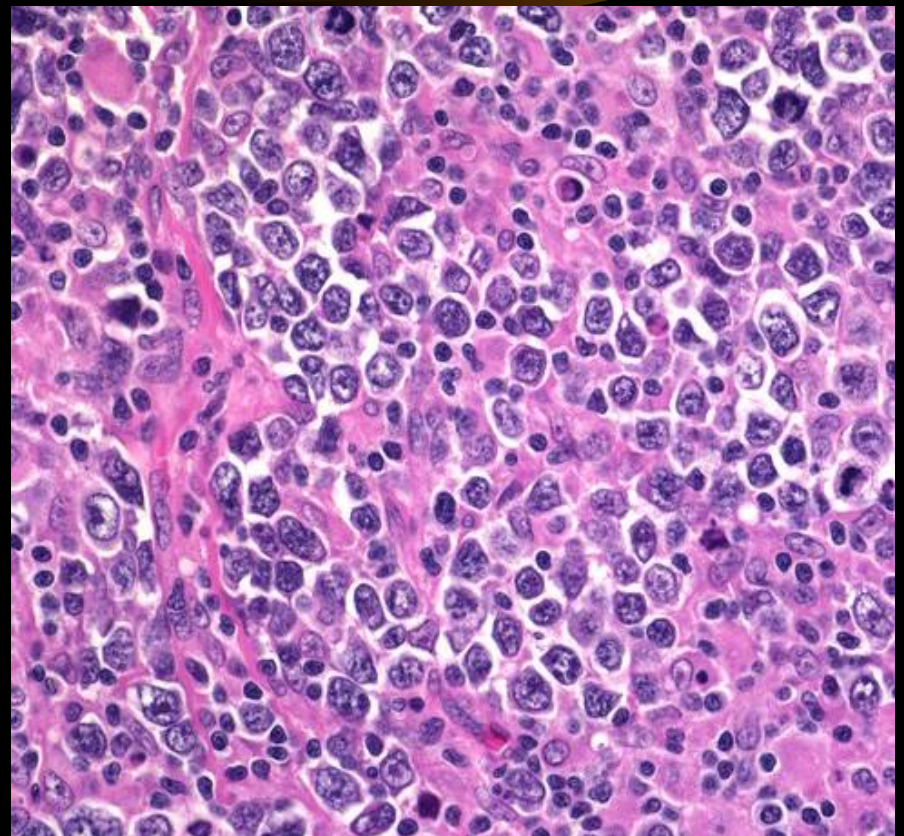
# *Grading*

- Histologic description based on cell morphology, independent of phenotype (B-cell or T-cell).
- Low, intermediate, and high-grade
  - cellular size
  - mitotic indices
- National Cancer Institute Working Formulation (NCI-WF)

# *Ferret Lymphoma*

## *Classification: Grading*

- Cell Morphology
  - Small, medium, large
  - Blast vs mature
  - Monomorphic/polymorphic
- Nucleus
  - Chromatin
  - Mitotic index



# *Ferret lymphoma classification: Phenotyping*

- Defines tumor etiology
  - B-cell or T-cell in origin.
- Requires immunohistochemical stains or flow cytometry
  - CD3 : T-cell marker
  - CD79 $\alpha$  : B-cell marker
- Not routinely assessed in ferrets at this time.

## *Examples*

- Stage: I, alimentary; Grade: small-cell, low mitotic activity, round nuclei, indistinct nucleoli
- Stage: IV, multicentric; Grade: large-cell, intermediate mitotic activity, round nuclei, distinct nucleoli



# *Descriptive Literature*



# *Ferret Lymphoma*

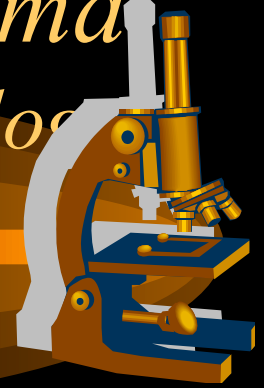
## *Etiology*

- Spontaneous
- Viral
  - Ferret Cluster Cases
  - Proposed Viral Agents
    - Aleutian Disease Virus
    - FeLV
    - Other retrovirus



# *Ferret Lymphoma*

## *Viral Etiology*



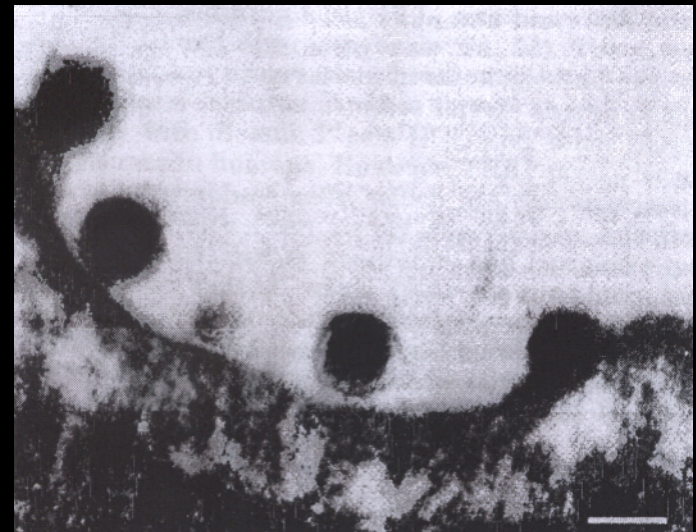
### Erdman et al 1995

- (n = 6)
- 4yr FS lymphoma (leukemic)
- IP Inoculates
  - Fresh whole cells (n=2)
  - Frozen whole cells (n= 2)
  - Filtered supernatant (n = 2)

# *Ferret Lymphoma*

## *Erdman et al 1995*

- 2 euthanized
- 3 of 4 developed disease
  - polymorphous lymphoma
  - Tissue Analysis: Increased RT activity
  - Electron Microscopy: Type C retrovirus-like particles
  - Koch's Postulates?
  - Controls?



# *Ferret Lymphoma*

- Literature: Clinical Disease



# *Ferret Lymphoma*

*(Erdman et al 1996)*

- Erdman et al 1992 (n = 19)
- Erdman et al 1996 (n = 60)
  - Age: <1 yr to 8 yr
  - Sex: M 36, F 29
- Clinical signs: Variable
- Younger ferrets vs. Older Ferrets
  - Acute onset
  - Multicentric distribution
  - Mediastinal mass
  - Lymphocytosis

# *Ferret Lymphoma*

## *Clinical Disease: Literature Review*

- **Adult (lymphocytic) form**
  - Most common variant
  - Age 2-9 years
  - PLNs most common clinical sign
  - Longer survival times
- **Juvenile (lymphoblastic) form**
  - < 2 years
  - Organomegaly (liver, spleen, thymus)
  - Bone marrow infiltration
  - Short survival times
- perpetuated throughout the literature

# *Ferret Lymphoma*

## *Clinical Disease: Literature Review*

- Immunoblastic polymorphous form
  - Visceral organs
  - Short survival time
  - Mid-western U. S.
- Other forms



# *Ferret Lymphoma Classification*

- Other Disease Associations
  - Cutaneous, epitheliotropic
  - *Helicobacter mustelae* associated gastric lymphoma
  - Orbital lymphoma
  - Lymphoplasmacytic keratitis
  - Hypereosinophilic Syndrome associated



# *Ferret Lymphoma: Clinical Presentation*



- There is no universal signalment or clinical presentation for lymphoma in ferrets.

# *Lymphoma in Ferrets*

## Clinical Perspective at Gulf Coast



# *Ferret Lymphoma Diagnostics*

- According to Clinical Signs
  - CBC
  - Chemistry Panel
  - Bone Marrow
  - Imaging
    - Radiographs
    - Ultrasound
  - Microscopic evaluation
    - Fine Needle Aspirates (fluid or tissue)
    - Biopsy
  - Immunohistochemistry



# *Ferret Lymphoma Retrospective Study*

- N = 32
- 13 Males, 19 Females
- Age
  - Range: 6 mo to 7.5 years
  - Mean (years) : 4.6 ( $\pm$  1.8)
- Survival Time
  - Range: 0 to 1199 days
  - Mean (days): 242 ( $\pm$  315)
- Diagnosed by FNA + IHC or Biopsy
- Confirmed with necropsy



# *Ferret Lymphoma*

## *Common Clinical Presentations*

- Lethargy
- Anorexia
- Dyspnea
- Coughing
- Weight Loss
- Hematochezia
- Vomiting
- Diarrhea



# *Ferret Lymphoma*

## *Common Physical Exam Findings*

- Pale mucous membranes
- Abdominal Mass/  
Organomegaly
- Peripheral lymphadenopathy



# *Ferret Lymphoma Retrospective Study: All Ferrets*

## Presenting Findings

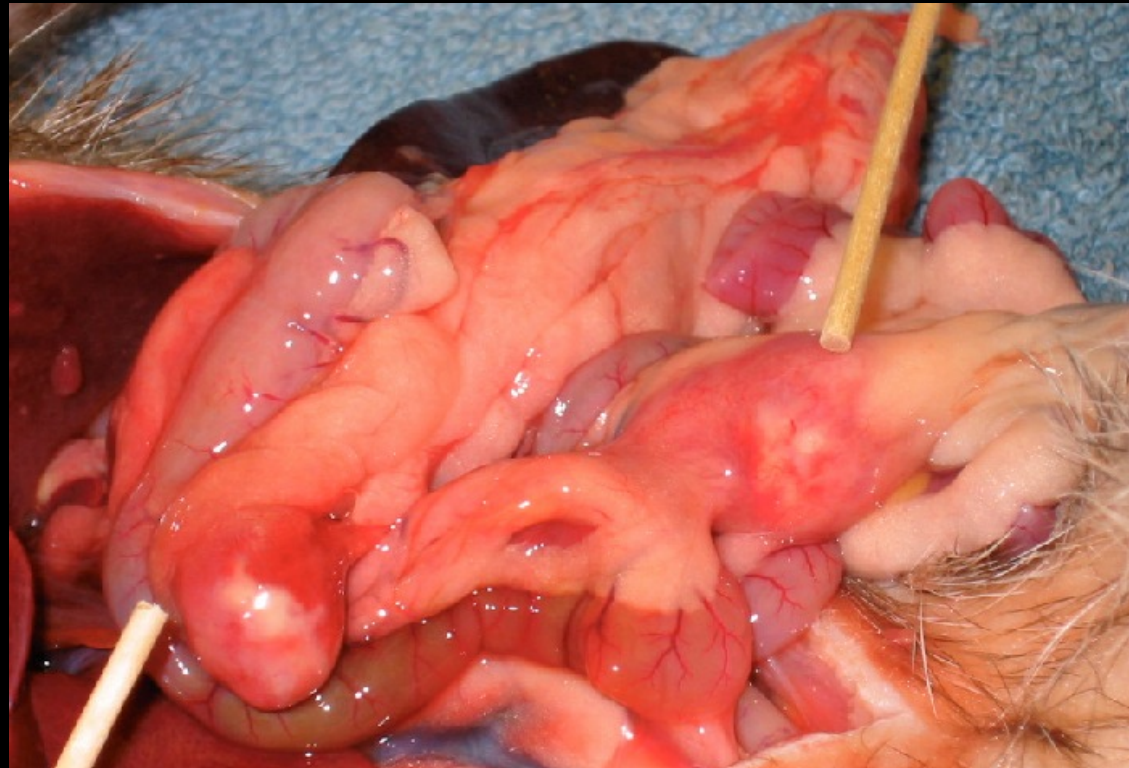
- Palpable Abdominal Masses (21/30) 70%
- Peripheral Lymphadenopathy (12/31) 38%
- Incidental Finding (7/31) 23%
- Thoracic Symptoms (6/31) 19%



# *Ferret Lymphoma*

## *Incidental Finding*

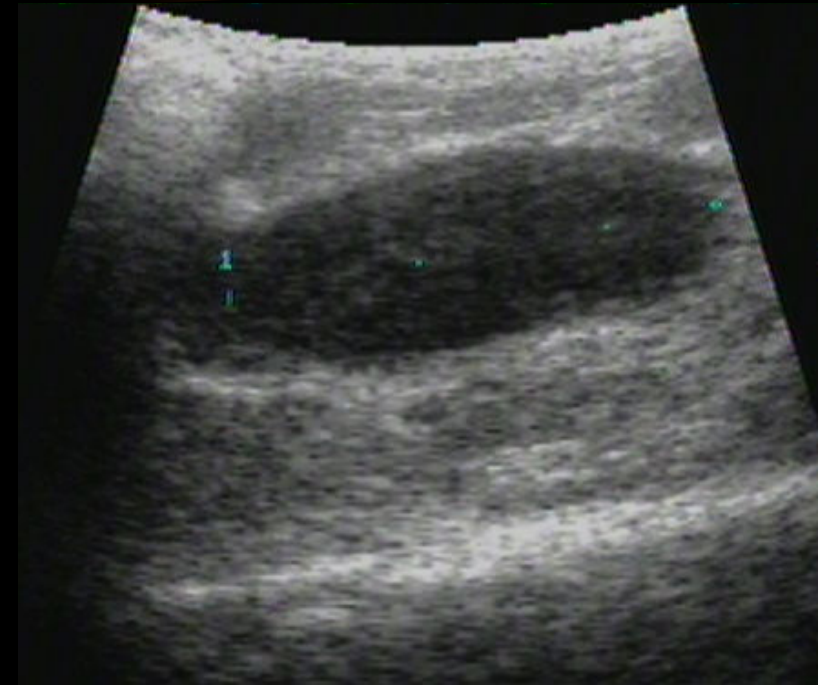
Incidental Finding at Surgery or Ultrasound  
Mesenteric Lymphadenopathy



# *Ferret Lymphoma*

## *Retrospective Study: All Ferrets*

- Abdominal Ultrasound (n = 27)
  - Mesenteric Lymphadenopathy 100%
  - Abdominal Organ Involvement (15/27) 55%
    - Spleen 9/15
    - Liver 4/15
    - Intestine 2/15



# *Ferret Lymphoma Retrospective Study: All Ferrets*

- Hemogram (n = 30)
  - Anemia (HCT <40) (11/30) 36%
  - Leukopenia (3/30) 10%
  - Leukocytosis (7/30) 23%
    - Neutrophilia (4/7)
    - Lymphocytosis (2/7)
    - Eosinophilia (1/7)

# *Ferret Lymphoma Retrospective Study: All Ferrets*

- Chemistry Panel (n = 26)
  - Liver enzymes 12%
  - Kidney values 19%
  - Calcium (less than 12) 11%

# *Ferret Lymphoma Retrospective Study: All Ferrets*

## Cytology

- n = 27
- Immature Cells: Blasts, Prolymph 59%
- Mature Lymphocytes 23%
- Pleiomorphic, Intermediate 18%
- Only 3 ferrets < 2yrs of age!

## *New Literature:*



- All multicentric lymphomas identified were comprised of blast cells, largely occurring in adult ferrets.

Onuma M, Kondo H, Ono S, et al. Cytomorphological and immunohistochemical features of lymphoma in ferrets. *J Vet Med Sci* 2008;70:893-898.

## *New Literature:*

- Visceral involvement in almost all ferrets
- Several ferrets representing all age groups had larger blast-like variants
- Peripheral lymphadenopathy rare
- Correlation of the blast form to young ferrets was absent.

Ammersbach M, DeLay J, Caswell JL, et al. Laboratory findings, histopathology, and immunophenotype of lymphoma in domestic ferrets. *Vet Pathol* 2008

# *Ferret Lymphoma*

## *Clinical Disease: Literature Review*

- **Adult (lymphocytic) form**
  - Most common variant
  - Age 2-9 years
  - PLNs most common clinical sign
  - Longer survival times
- **Juvenile (lymphoblastic) form**
  - < 2 years
  - Organomegaly (liver, spleen, thymus)
  - Bone marrow infiltration
  - Short survival times
- **perpetuated throughout the literature**



## *Conclusion*



- The age of ferrets cannot be reliably used to determine type, extent, or prognosis for lymphoma.



# *Ferret Lymphoma Treatment Literature*

- Dugan et al 1989
  - Case report: 2.5 yr mediastinal mass, spleen
  - L-asparaginase, cyclophosphamide, prednisone
  - Complete remission 11 months
- Hutson et al 1992
  - COP protocol, Radiation, doxorubicin
  - Survival 23 months

# *Ferret Lymphoma Treatment Literature*

- Erdman et al 1996 (n = 60)
  - Chemotherapy (n = 22)
    - 3 mortalities due to pancytopenia
    - (n = 13) Mean survival 10.6 months
  - Surgery
    - (n = 7) Mean survival 12 months
  - No treatment
    - (n = 4) Mean 3.1 yrs, range 1.3-5.2 yrs



# *Ferret Lymphoma Treatment*



- No Studies to Date Evaluating or Comparing Established Treatment Protocols

# *Lymphoma in Ferrets*

## Treatment Perspective at Gulf Coast



# *Ferret Lymphoma Treatment at Gulf Coast*

- Minimal: Prednisone
- Chemotherapy
  - Cytosin
  - L-asparaginase
  - Vincristine
  - Rescue Drugs: Adriamycin
- Radiation (Focal or ½ body)
- Aggressive Combination

# *Ferret Lymphoma Treatment at Gulf Coast*

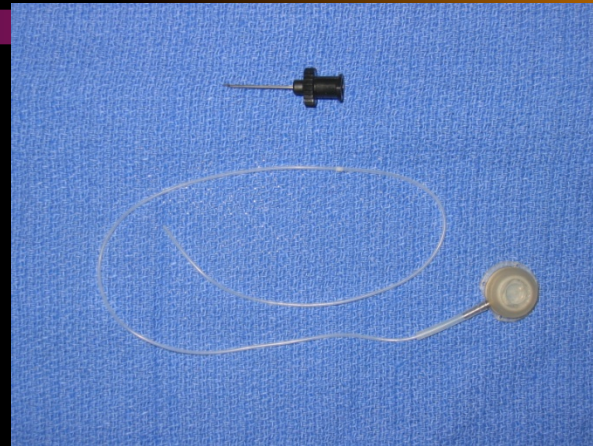
- Reported Treatment Challenges
  - Catheter placement
    - Size of patient
    - Patient Compliance
  - Side Effects
    - Cytopenias
    - Hair loss
    - Vomit, diarrhea, others





# *Ferret Lymphoma Treatment at Gulf Coast*

- Intravenous Administration
  - Catheter placement
    - Sedate
  - Vascular Access Port
    - Allows Repeated Administration
    - No sedation



# *Ferret Lymphoma Study Treatment Groups*

1. Minimal Treatment
  - 1-2 mg/kg PO BID Prednisone
2. Palliative Chemotherapy
  - 1-2 mg/kg PO BID Prednisone
  - 10 mg/kg Cytoxan
  - +/- L-asparaginase 400 IU/kg
3. Aggressive Chemotherapy (COP)
  - 1-2 mg/kg PO SID or BID Prednisone
  - 10 mg/kg Cytoxan PO
  - 0.12 mg/kg Vincristine IV weekly
  - +/- L-asparaginase 400 IU/kg IM
4. Radiation + Chemotherapy (COP)

# *Ferret Lymphoma Study*

## *Mean Survival Time: Preliminary Data*

	Mean (days)	SD	Median
• Prednisone (n= 5)	23	<u>±</u> 43	3
• Pred/Cytox (n = 7)	117	<u>±</u> 181	24
• COP (n = 9)	437	<u>±</u> 408	211
• COP + Rad (n = 3)	216	<u>±</u> 233	129
• Radiation (n = 2)	208	+290	208

# *Ferret Lymphoma Study*

## *Aggressive Chemotherapy*

- No mortalities associated with chemotherapy
- Leukopenia (7/12) 58%
- Complications
  - Pneumonia
  - UTI
  - Sepsis



# *Ferret Lymphoma Study*

## *Subjective Clinical Improvement\**

- Prednisone (n= 4)      0%
- Pred/Cytox (n = 7)      33%
- COP (n = 7)      85%
- COP + Rad (n = 3)      100%
- Radiation (n = 2)      50%

– \*according to owners' observations

# *Ferret Lymphoma Study*

## *Preliminary Survival Data*

	Mean	SD	Median
• Clinical Findings			
– Incidental (n = 6)	135	<u>±</u> 151	80
– Non-incidenta (n = 19)	238	+343	88
• Cell Type			
– Mature (n = 5)	172	+154	161
– Immature/Blast (n = 13)	229	+309	39
• Juvenile vs Adult			
– Only three ferrets < 2 years			

# *Ferret Lymphoma Study*

- Further Analysis
  - “Benchmark” analysis
  - ANOVAs
  - Predictive values
    - Gender
    - Age
    - Cell Type



# *Ferret Lymphoma Study Limitations & Future Studies*



- Limitations

- Staging
- Protocol Standards
- Control Group
- Sample Size
- Regional  
Distribution

- Future Studies

- Increase Sample Size
- Regional Diversity
- Immunohistochemistry
- Viral vs Spontaneous
- Others...



## *Fact or Fiction?*

- Most ferrets with lymphoma have big peripheral lymph nodes
- Ferrets with lymphoma commonly have high lymphocyte counts
- There is a “better” protocol to treat lymphoma

## *Fact or Fiction?*

- Young ferrets with lymphoma get a worse form with a worse prognosis and shorter life expectancy
- Older ferrets get a chronic form that doesn't respond well to treatment
- Ferrets with lymphocytic leukemia (bone marrow) have the worst prognosis

# *Ferret Lymphoma Study*

## *CONCLUSIONS*

1. Recommended classification scheme for ferrets:  
stage and location
2. Lymphoblastic disease is not limited to juvenile ferrets
3. Most common physical exam finding:  
abdominal mass
4. Most common hematologic abnormality: anemia

# *Ferret Lymphoma Study*

## *CONCLUSIONS*

5. Lymphocytosis and peripheral lymphadenopathy are inconsistent in this disease
6. Ferrets treated with aggressive chemotherapy and radiation have a longer survival time than those treated with palliative therapy
7. Subjective improvement >85% of ferrets treated with aggressive chemotherapy

*Questions?*

