Ferrets have been used as a research model for neoplasia due to their predilection to produce tumors similar to humans. Lymphoma is the most common malignant neoplasia in domestic ferrets, Mustela putorius furo. Adrenal tumors are more common but commonly due to reproductive dysfunction and not a true neoplastic disease. Knowledge of how to definitively diagnose the type of lymphoma, which dictates the chemotherapy used or possibly no chemotherapy at all, is critical to successful therapy. Lymphomas can be classified by age of onset, affected organs, cell morphology, and immunophenotype.

Age can be used to prognosticate lymphoma quickly but thorough investigation and accurate diagnosis is required for best outcome. Acute onset, mediastinal mass, lymphocytosis, and multicentric distribution have been linked with younger ferrets, and lymphopenia, lymphadenopathy and survival longer than 2 months after diagnosis was associated with older ferrets. Peripubescent ferrets had rapidly progressive stage IV high grade immunoblastic or small non-cleaved cell lymphoma. Adult ferrets had stage II or IV low grade diffuse small lymphocytic (DSL) lymphoma, stage IV high grade small non-cleaved cell lymphoma, or stage IV high grade immunoblastic polymorphous (IBP) lymphoma.

There are three main forms of lymphoma that have predilection for different anatomic sides.

1. Peripheral lymphadenopathy
   a. Typically adult onset
   b. Multiple types but typically T cell
   c. Better prognosis
2. Mediastinal/Mesenteric/Multicentric
   a. Lymphoblastic lymphoma – T cell
   b. Juvenile onset
3. Splenic
   a. Normal spleen weight is 0.5% to 1.3% of a ferret’s body
      i. Increase percentage warrants histopathology at necropsy
4. Gastric
   a. Any age but older more common
   b. Associate with Helicobacter pylori
   c. B cell neoplasia with helper T cells contributing to disease.
5. Skin
   a. Rare Sezary syndrome reported

Diagnostic Imaging

Imaging lesions were predominantly detected in the abdomen, and most frequently included intra-abdominal lymphadenopathy (12/14), splenomegaly (8/14), and peritoneal effusion (11/14). Lymphadenopathy and mass lesions were typically hypoechoic on ultrasound. Mild peritoneal effusion was the only detected abnormality in two ferrets. Mild pleural effusion was the most common thoracic abnormality (3/12). Expansile lytic lesions were present in the vertebrae of two ferrets with T3-L3 myelopathy and the femur in a ferret with lameness.

T versus B cell

When gastric lymphoma is excluded, a predominance of T cell lymphoma is diagnosed. Immunohistochemical examination of 18 specimens, excluding 2 insufficient specimens, showed that 16 (88.9%) and 2 (11.1%) lymphomas were of T-cell origin and B-cell origin, respectively. When mediastinal lymphomas of Marshall Farms ferrets were typed, 90% represented aggressive small cleaved, T cell lymphoma. Remnants of thymic tissue were found in all T cell lymphomas indicating a thymic origin and predilection for thymic lymphoma over thymoma which is rarely diagnosed in ferrets.

GASTRIC

Gastric lymphoma are typically diagnosed in the lesser curvature of the stomach wall and are predominantly IgG positive indicating a B cell origin. These B cells are most commonly Kappa positive. A link of Helicobacter pylori with gastric MALT lymphoma was first suggested in 1991 by identification of the bacteria in the vast majority of patients. This is the typical site of Helicobacter pylori infection.
Histologically, uninfected ferret stomachs are typically devoid of lymphoid follicles. Upon infection with *H. pylori*, lymphoid follicles become prominent. An appropriate inflammatory response to the infectious agent must be differentiated from neoplastic cells. This is done by evaluating clonality of the Kappa and Lambda chains using polymerase chain reaction. As in humans, ferrets typically have a 1:1 Kappa:Lambda ratio. Immunohistochemically, the neoplastic cells of MALT lymphoma are usually CD20+, CD79a+, CD5-, CD10-, CD23-, CD43+/-, cyclin D1-. Cytogenetic analyses using G-banding, reverse transcription polymerase chain reaction and/or fluorescence in situ hybridization for t(11;18)/API2-MALT1 or other chromosomal translocations are also useful for confirming the diagnosis.

In *H. pylori*-dependent cases, microbe-generated immune responses, including interaction between B and T cells involving CD40 and CD40L co-stimulatory molecules, are considered to induce the development of MALT lymphoma. Laboratory studies demonstrated that the growth of neoplastic B cells is stimulated by tumor-infiltrating *H. pylori*-specific T-cells, which require interaction between B and T cells involving CD40 and CD40L co-stimulatory molecules[14-19]. Thus, the genesis of *H. pylori*-dependent gastric MALT lymphoma is now considered as follows: an *H. pylori* infection results in T cell dependent responses through the classic germinal center reaction, and thus generates reactive B and T cells. The *H. pylori*-specific T cells raised in the reactive component then migrate to the marginal zone/tumor area and provide non-cognate help to autoreactive neoplastic B cells, which may involve stimulation of CD40 and other surface receptors by soluble ligands and cytokines.

In humans, approximately 90% of patients with gastric MALT lymphoma are infected with *H. pylori* and about 70% of the cases respond to *H. pylori* eradication. Exact numbers are not as well established in ferrets but are similar. Therefore, chemotherapy is NOT recommended unless treatment for *H. pylori*. Treatment for *H. pylori* may include amoxicillin (20 mg/kg [9.1 mg/lb], PO, q 12 h), metronidazole (20 mg/kg, PO, q 12 h), and famotidine (0.5 mg/kg [0.23 mg/lb], PO,q 24 h)

In *H. pylori*-independent cases, activation of the nuclear factor-κB pathway by oncogenic products of specific chromosomal translocations such as t(11;18)/API2-MALT1, or inactivation of tumor necrosis factor alpha-induced protein 3 (A20) are considered to contribute to the lymphomagenesis. Radiotherapy is highly effective in localized cases (stage 1/II). While chemotherapy and immunotherapy with rituximab are also effective, these systemic treatments are suitable for cases with an advanced stage. Because of the indolent behavior of MALT lymphoma, the strategy for patients not responding to *H. pylori* eradication should be tailored in consideration of the clinical stage and extent of the disease. (Nakamura) Extramodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma is an indolent non-Hodgkin lymphoma derived from marginal zone B-cells, which occurs in a number of extranodal organs, including the gastrointestinal tract, lung, salivary gland, thyroid, ocular adnexa, liver or skin.

Other

Large granular cell lymphoma has also been reported with the spleen believed to be the origin, similar to the dog. These cd3+ tumors are believed to represent in vivo-activated cytotoxic T lymphocytes. Features of this form of leukemia include moderate lymphocytosis with an increase in the number of large granular lymphocytes, severe neutropenia, rheumatoid arthritis, and, less frequently, anemia and thrombocytopenia. These tumors in ferrets do not typically enter the GI tract as in cats, but follow a more common leukemic course as seen in dogs with origin in the spleen and spread to the bone marrow, peripheral blood, and liver.

Osteolytic plasma cell tumor consistent with multiple myeloma has been reported in low numbers of ferrets. (Eshar) Bones with lytic lesions previously reported include long bones and vertebra. Hematologic and biochemical abnormalities including hypoalbuminemia,hyperglobulinemia, hypercalcemia, hypocholesterolemia, anemia, and thrombocytopenia reflect abnormalities reported for other small animals with multiple myeloma. Immunohistochemical analysis revealed multifocal CD79α-staining neoplastic cells throughout the mass and rare BLA36-staining cells; the neoplastic cells uniformly lacked staining for CD3. On the basis of these histological findings, a diagnosis of plasmablastic lymphoma was made. Interestingly, MUM1 was negative, however, the positive control was also negative indicating poor crossreactivity in ferrets. Chemotherapy for the ferret’s lymphoma was initiated 1 week after surgery

Tuft’s University Protocol for treatment of Ferret Lymphoma

**Week/Drug Dosage**

<table>
<thead>
<tr>
<th>Week</th>
<th>Drug Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>l-asparaginase 10,000 U/m2, SC</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide 200 to 250 mg/m2 in 50 mL of lactated Ringer’s solution/kg, SC</td>
</tr>
<tr>
<td>2</td>
<td>l-asparaginase† 10,000 U/m2, SC</td>
</tr>
<tr>
<td>3</td>
<td>l-asparaginase 10,000 U/m2, SC</td>
</tr>
<tr>
<td></td>
<td>Cytosine arabinoside 300 mg/m2 (each 100 mg diluted in 1 mL of water), SC, once daily for 2 days</td>
</tr>
<tr>
<td>4</td>
<td>None† NA</td>
</tr>
</tbody>
</table>

None† NA
5 Cyclophosphamide 200 to 250 mg/m² in 50 mL of lactated Ringer’s solution/kg, SC
7 Methotrexate† 0.8 mg/kg, IM or SC
8 None† NA
9 Cyclophosphamide 200 to 250 mg/m² in 50 mL of lactated Ringer’s solution/kg, SC
11 Cytosine arabinoside 300 mg/m² (each 100 mg diluted in 1 mL of water), SC, once daily for 2 days
Chlorambucil One 2-mg tablet once or half a tablet for 2 days, PO
12 None†
13 Cyclophosphamide 200 to 250 mg/m² in 50 mL of lactated Ringer’s solution/kg, SC
14 None† NA
15 Procarbazine 50 mg/m², PO, once daily for 14 days
16 None† NA
17 None† NA
18 Cyclophosphamide 200 to 250 mg/m² in 50 mL of lactated Ringer’s solution/kg, SC
20 Cytosine arabinoside 300 mg/m² (each 100 mg diluted in 1 mL of water), SC, once daily for 2 days
Chlorambucil One 2-mg tablet once or half a tablet for 2 days, PO
23 Cyclophosphamide 200 to 250 mg/m² in 50 mL of lactated Ringer’s solution/kg, SC
26 Procarbazine 50 mg/m², PO, once daily for 14 days
27 None‡ NA

*In addition to the drugs listed, prednisone (40 mg/m², PO, q 24 h) should be administered as a baseline medication. †During the indicated week, a CBC should be performed to monitor the ferret’s status. If the hemogram suggests severe myelosuppression, reduce the dosage of the affecting drug by 20% to 25% for the next treatment. ‡During the indicated week, a CBC and serum biochemical analysis should be performed. If the ferret is not in remission at week 27, continue chemotherapy for weeks 19 to 25 for 3 cycles.

Prednisone has been noted to cause severe PU/PD and dehydration at this dosage as well as diarrhea treated with antibiotics. Cyclophosphamide has caused severe leukopenia and neutropenia with the recommend to skip chemotherapy and discontinue this medication.

Treatment for lymphoma in ferrets has included radiation therapy, tumor excision, various chemotherapeutic regimens, and combination therapy. Reported survival time for ferrets receiving chemotherapy for lymphoma ranges from 11 to 24 months. Often the response to therapy is unpredictable, as some ferrets can live up to 2 years after diagnosis without treatment, whereas others might die within 2 weeks after diagnosis despite receiving chemotherapy.

REFERENCES


