

Last Dance – Malignant Lymphoma in Ferrets

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Lymphoma – a swift silent killer. One day your ferret appears happy and healthy; the next day you notice a small hard lump under the jaw or by the leg. After a quick trip to the vet, you learn the sad truth – your beloved friend will soon be a cherished memory.

In this third article on neoplasia in ferrets, let's look at lymphoma - what it is, how it progresses so quickly, and why the results are so often tragic.

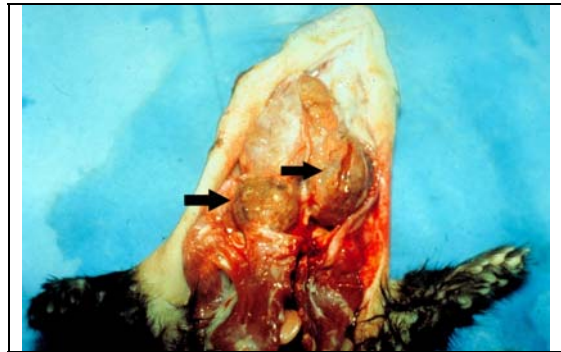
Lymphoma is a **neoplasm**, an abnormal proliferation of cells beyond the body's normal control mechanisms. In this case, lymphocytes, the cells which populate lymph nodes and control and execute many functions of the body's immune system are the cells whose proliferation has gone haywire. Beyond this, lymphoma (also known as lymphosarcoma or malignant lymphoma) is a **malignancy**, a neoplasm with the ability to grow at an accelerated rate as well as to transplant itself to other organs through the blood or lymph channels, as small pieces break off from a large tumor (a process known as metastasis.)

Lymphoma is a common occurrence in ferrets. Overall, it is the third most common neoplasm overall in ferrets (following insulinoma and adrenal neoplasms) and the most common of all malignancies. And it doesn't discriminate based on age - while the majority of cases affect animals 5 years and older, animals may be affected as young as 4 months of age.

While a few similarities exist, as outlined below, lymphoma is unique in its **dissimilarity** between cases. Every case is unique and unpredictable – which organs are affected, how rapidly the disease progresses, etc. The tumor may choose to infiltrate critical organs such as the brain, kidneys, or heart, or non-critical areas such as the eyes or skin. To complicate matters, it most

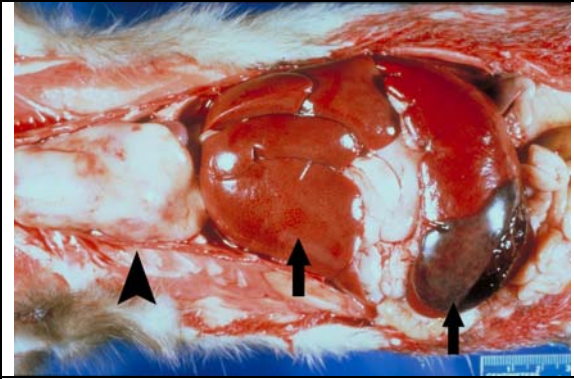
often hits multiple organs at the same. Affected animals may die suddenly with no signs, or may live for years. For these reasons, lymphoma is the “great impostor” of ferrets – it may look like a number of other disease, and should be included in the rule-out list for any significantly ill ferret.

Let's look at the basics of lymphoma. In the ferret, three major forms of lymphoma exist, which generally differ from each other in terms of age of animal affected, the organs affected, the average survival time, and the predicted response, if any, to therapy.



Note the markedly enlarged cervical lymph nodes in a 5-year-old ferret with adult-onset malignant lymphoma (arrows). These lymph nodes were approximately golfball-sized and rock hard. They were considerably smaller at the time of diagnosis, but this animal was treated with palliative therapy for three months.

The most common form of lymphoma in our domestic ferrets is the lymphocytic form (also known as the adult-onset form.) In this form, which is most common in animals over the age of 2 years, neoplastic lymphocytes first proliferate within the lymph nodes. If the peripheral nodes (the lymph nodes present “on the outside” of the body - the angle of the jaw, neck, around the front legs, hind legs, and behind the knee) are affected, signs of disease may be spotted quickly. However, if the mesenteric nodes (the lymph nodes within the abdomen) are affected first, the condition may not be identified until late in the course of disease. In this form, the neoplastic lymphocytes strongly resemble normal lymphocytes in most respects, including their slower rate of division – meaning that the progression of this disease is the slowest of any form, and survival times are the longest (averaging about 4 months after diagnosis.) Rarely, untreated adult-onset cases may proceed for up to a year with waxing and waning signs before a sudden downturn is observed.



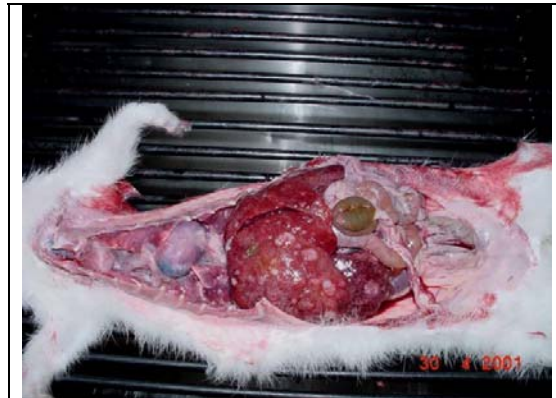
This photo shows a typical presentation of juvenile-onset lymphoma. At left, a large white neoplasm replaces the thymus and occupies almost the entire thoracic cavity (arrowhead), displacing and compressing the lungs. The liver (center arrow) and spleen (right arrow) are also markedly enlarged. The dark area on the lower portion of the spleen is a splenic infarct – an area of dead tissue, killed by the marked decrease in local blood supply due to the growing splenic neoplasm.

A second form, lymphoblastic lymphoma (also called the **juvenile** form) usually affects ferrets **less** than two years of age. In this variant, myriads of immature (blastic) cells infiltrate visceral organs in large numbers, while the lymph nodes remain unaffected until the latest stages of disease. Infiltration by neoplastic cells results in enlargement of major organs and the most commonly affected organs are the liver, spleen and thymus. In most cases, thymic enlargement rapidly becomes a life-threatening issue, as the thymus occupies the thoracic cavity, a space enclosed by the unforgiving cage of the ribs. As the neoplastic cells expand the thymus (as seen in Figure 2), the thymus compresses the adjacent lungs, making it difficult, and eventually impossible, for the animal to breathe. In juvenile lymphoma, labored breathing is often the first clinical sign noticed by the owner, and this form's early compromise of pulmonary function is the reason that it carries the shortest survival time of all variants (only 2 weeks after diagnosis.)

The third and last common variant is the immunoblastic-polymorphous variant (a mouthful of a name based on the microscopic appearance of the cells), a highly aggressive form with rapid cell proliferation and no distinct organ, node, or age predilection. For unknown reasons, this form is most commonly seen in the Midwestern United States. An interesting finding in this form is the microscopic similarities to virally-induced forms of

lymphoma in other species (including man and rabbits.) In fact, in 1995, researchers at the Massachusetts Institute of Technology were able to transmit lymphoma between ferrets with cell-free extracts, suggesting a possible viral cause for lymphoma, or at least some forms of it. The development of lymphoma in this experiment took several years in inoculated individuals, and not all inoculated ferrets developed lymphoma, but the results of this study are too intriguing to ignore. To date, however, a virus has yet to be identified or isolated from malignant lymphoma in ferrets.

The diagnosis of most cases of lymphoma begins with the identification of appropriate clinical signs. Sometimes, there are no premonitory signs or apparent clinical signs, and animals are simply found dead. Occasionally, clinical signs of lymphoma are attributed to other previously diagnosed conditions, such as insulinoma or cardiomyopathy.



This immunoblastic-polymorphous lymphoma shows whitish nodules in the liver and other organs, which represents foci of lymphoma. In such cases, it is often difficult to ascertain in which organ the tumor arose.

Adult-onset cases are often diagnosed when one or more lymph nodes swells and hardens. It might affect all nodes at once or just one, with enlargement of additional nodes over time. (Occasionally the accumulation of fat around lymph in geriatric ferrets may lead to errant clinical diagnosis of lymphoma – in general, fat surrounding nodes feels squishy, while lymphoma feels like a marble.) This is only one of many cogent reasons why the diagnosis of lymphoma should not be based on overall clinical impression, but **always** by direct microscopic examination of affected tissue -- the second, and most important step. Examination of a surgically excised lymph node or piece of suspect organ tissue is best, but at a minimum, aspiration of an affected node or organ with a

needle and syringe is required. This examination should be performed by a pathologist with experience in ferret tissues, as this diagnosis is often not straightforward, and can be quite tricky.

Other tests may contribute useful information, but are not diagnostic in themselves. Radiography is often helpful in juvenile lymphoma or adult-onset cases which do not result in obvious enlargement of peripheral nodes. The enlargement of internal organs, especially thymus is strongly suggestive of lymphoma; however other disease processes may result in abnormal size of internal organs. The most common example of this is the spleen – 95% of enlarged spleens are the result of chronic GI inflammation, and not neoplasia. For this reason, aspirate of affected organs should always be performed to confirm that the cause of organ enlargement is malignant lymphoma rather than some other cause.



The spleen ruptured due to a malignant lymphoma and splenic palpation during physical examination. While it is likely that this animal would have died within weeks, the hemorrhage induced by normal veterinary examination of this spleen (rendered brittle by the infiltration by lymphoma) resulted in death within hours.

Bloodwork, which may be helpful in some cases, rarely pinpoints a diagnosis on its own. Far less than 10% of lymphomas are leukemic (when neoplastic cells are seen in the blood). In cases of lymphocytic leukemia, in ferrets, elevation of lymphocytes numbers may be mild, and the cells will look perfectly normal, making this a very difficult diagnosis for most practitioners.

A common misconception, and often tragic misconception among veterinarians is that elevated levels of lymphocytes in the blood is a hallmark of lymphoma in the ferret. The truth is

that chronic inflammation of the GI tract, as seen in ferrets with several common syndromes such as *Helicobacter mustelae* infection, inflammatory bowel disease, or ferret coronavirus (ECE) is a far more common cause of this finding than lymphoma. In most cases of lymphoma, bloodwork is often not helpful until neoplastic infiltration of a particular organ (liver, kidney, etc.) pushes it to the level of failure. At this point, organ-specific changes in blood values may be seen, but it still remains for the veterinarian to prove that lymphoma is the culprit.



This photo shows cutaneous lymphoma in a 2-year old ferret. This large lesion is typical, although angry and infiltrative-appearing. Complete surgical examination resulted in this animal's survival for years after the diagnosis. The original lesion required two surgeries for complete excision. (Photo courtesy of Betty Janner).

But the news gets worse. Treatment options for affected ferrets are still limited, and only 10% will respond to traditional chemotherapy (and it is likely that a significant percent of this number may have been incorrectly diagnosed with the disease). Two potential treatments exist – chemotherapy or palliative therapy. Most vets agree that unfortunately, the long-term survival rates do not differ significantly between these two approaches.

Traditional chemotherapy involves the intravenous administration of cell-killing agents at precise intervals – a process designed to effect maximal killing of neoplastic cells while inducing minimal killing of the body's normal cells. Owners should be firmly committed to the requirements of proper chemotherapy protocols prior to embarking on a regimen – there is no casual approach to these treatments. Chemotherapeutic drugs and dosages are specific, and any deviation from accepted combinations or regimens will often result a poor outcome. These regimens require multiple

weekly trips to the vet (which decrease over time if remission is achieved), intravenous catheter or vascular port placement, and often significant cost. In actual fact, this approach is not often attempted due to the limited chance of success and the possible negative impact on quality of life for a patient with a poor prognosis.

Palliative treatment involves daily oral dosing of affected animals with high doses of corticosteroids, usually prednisone. Initially, high doses of steroids result in a decrease in tumor burden, a shrinkage of affected nodes and organs, and significant temporary improvement. But palliative therapy, as encouraging as it may initially be, should only be considered a temporary fix, as the neoplasm inevitably breaks through even maximal doses to return with a vengeance. The tumor regrows, and the animal's clinical condition deteriorates rapidly. Yet, in most cases, several "good" months are attained in this fashion.

My general recommendation to veterinarians dealing with malignant lymphoma is to offer a poor prognosis immediately upon diagnosis, and to hope that your patient proves you wrong. While it so rarely happens, I am always tickled to be proven foolish in these cases, and gladly trade a bruised ego for continued survival.

Not every case of lymphoma adheres to these rules, however. One particular form, that of primary cutaneous lymphoma (or a lymphoma that arises in the skin) is unique within our domestic pets. In this form, neoplastic lymphocytes generally remain restricted to the upper levels of the skin, and the progression is so slow that many cases may be treated successfully for years by surgically removing the tumors as they pop up. The key to this approach is rapid diagnosis and removal before the tumor spreads to a size or site where removal is untenable. Although the tumors may look very aggressive and angry (Fig 5), they can often be readily removed. One exception to this particular rule is cutaneous lymphoma's predilection to affect the feet, where there is little loose skin to remove. Many cases of lymphoma at these sites are often misdiagnosed or not diagnosed until large areas of skin on the feet are affected, so surgical treatment is untenable.

As a veterinarian who often deals with lymphoma, I often wonder what I can truly provide in the face of this dread disease, and I

usually come away with the same answer – a realistic appraisal without false hope. Ferret owners should understand fully the gravity of this diagnosis, so that they can enjoy what time is allotted to most animals with this condition. Some owners go to all lengths to effect treatment; Many seek herbal, dietary, or holistic cures, and the majority employ palliative therapy in order to enjoy the "last dance" with their pets. On a personal level, I've walked that road and danced that dance three times now with my own ferrets, and I consider my experience no different than most owners. Even though I am considered to be a ferret expert, there were no miracles for me (yet!), no prolonged remissions, but mercifully in two out of three, some time to say goodbye.

As readers of Ferrets Magazine know, I often try to approach these articles with humor, or at least optimism. I'm just happy to draw this one to a close.