AN UPDATE ON FERRET LYMPHOMA: A PROPOSAL FOR A STANDARDIZED CLASSIFICATION OF FERRET LYMPHOMA

Jörg Mayer, Dr Med Vet, MSc, Dip. ABVP (Exotic Companion Mammal), Dip. ECZM (Small Mammal), and Kristine Burgess, DVM, Dip. ACVIM (Oncology)

Abstract

Lymphoma is one of the most commonly diagnosed conditions in ferrets in the United States and in Europe. Despite the high frequency of occurrence, ferret lymphoma is poorly understood and is considered to be one of the more difficult diseases to diagnose accurately and successfully treat in these animals. An update on ferret lymphoma will be provided, along with a proposal to standardize a classification system for this common disease presentation. Copyright 2012 Elsevier Inc. All rights reserved.

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Lymphoma is reported to account for 10% to 15% of all neoplastic presentations in ferrets from the United States and Europe.[1,2] Improved diagnostic testing and increased reporting have likely contributed to the higher prevalence associated with this disease. Currently, the etiology of ferret lymphoma is unknown. Cluster outbreaks of lymphoma in ferrets are suggestive of an infectious etiology and, more specifically, a viral infection, but a true association continues to elude investigators.[3] It is tempting to designate a retroviral etiology as the underlying cause of ferret lymphoma because of its association with this disease in other animal species (e.g., cats and cattle). In cats and cattle, oncornavirus infection produces a distribution of lymphoid tumors that differs between juvenile and adult animals. Similar to young cats with feline leukemia, juvenile ferrets will commonly present with disease localized to the mediastinum. However, until a true association with a viral infection has been established in the ferret, the inciting cause of lymphoma in this species remains unidentified.

HISTORICAL CLASSIFICATION OF FERRET LYMPHOMA

Historically, 2 distinct forms of ferret lymphoma are described in the literature that are based on age and anatomic location. The juvenile (or lymphoblastic) form is thought to affect ferrets aged less than 2 to 3 years and involves infiltration of visceral organs by large lymphoblasts. Patients present with an acute, aggressive, multicentric form of lymphoma. This form of lymphoma is reported as rapidly progressive and uniformly fatal. In contrast, the lymphocytic form, or the adult/chronic presentation, occurs in ferrets aged greater than 3 years with a clinical history of markedly enlarged peripheral lymph nodes containing a homogenous population of small mature lymphocytes. Clinically, these animals often present with chronic, nonspecific signs such as weight loss and lethargy.[1]

The lymphoma classification described above appears to be an oversimplification for such a com-

From the Department of Small Animal Medicine and Surgery, College of Veterinary Medicine, University of Georgia, Athens, GA USA; and Cummings School of Veterinary Medicine, Tufts University, North Grafton, MA USA.
Address correspondence to: Jörg Mayer, Dr Med Vet, MSc, Dip. ABVP (Exotic Companion Mammal), Dip. ECZM (Small Mammal), Department of Small Animal Medicine and Surgery, College of Veterinary Medicine, University of Georgia, 501 D. W. Brooks Dr, Athens, GA 30602. E-mail: mayerj@uga.edu.

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plex disease. In our experience, ferrets diagnosed with lymphoma have variable clinical presentations as well as a diverse histologic pathology associated with affected tissues. Therefore, we propose a new system of lymphoma classification for ferrets to standardize diagnosis and ultimately guide in the selection of optimal treatment strategies.

HISTOLOGIC CLASSIFICATION AND IMMUNOPHENOTYPING

In 2002 the World Health Organization (WHO) published the Revised European-American Lymphoma (REAL) classification for domestic animals, which is adapted from human medicine to correlate histotypes with biological behavior.[4-7] The goal of this classification scheme is to create a standard for establishing a diagnosis, providing a reliable prognosis, and selecting efficient therapies for lymphoma cases. The WHO-REAL classification scheme described by Valli et al[6] is based on histologic characteristics including tissue architecture, nuclear size and shape, and immunophenotype. This system has recently been applied to evaluate clinical outcome in a retrospective study that showed that dogs with an indolent form of lymphoma (e.g., T-zone lymphoma, marginal zone, follicular lymphoma) will have a slower course of disease progression and treatment may not be necessary.[7,8] It is conceivable that ferret lymphoma can be classified according to a similar scheme, which may help to predict behavior of the disease and subsequent response to treatment.

The ideal workup for a staging process consists of a complete blood cell count (CBC), a biochemistry profile, urinalysis, whole-body radiographs (2 views), abdominal ultrasound, and bone marrow aspiration.

To determine cell immunophenotype, routine immunohistochemistry should be performed on affected tissue(s). The use of anti-CD3 and anti-CD79a antibodies is recommended to differentiate between B- and T-cell lymphoma in the ferret.[9] Although there is a paucity of information in the veterinary literature to show that immunophenotype correlates with disease prognosis in ferrets, one small study found that ferrets treated with chemotherapy survived an average of 4.3 months (T-cell lymphoma) or 8.8 months (B-cell lymphoma).[10] Additional information in the form of uniform diagnostic investigations and consistent treatments is required to better identify objective prognostic associations with ferret lymphoma tumor types.[10]

Preferably, classification of the lymphoma is accomplished through histopathologic evaluation of tissue samples. Although a fine needle aspirate may be useful, in humans with lymphoma, there is poor correlation of the WHO-REAL classification results between cytological and histopathologically derived samples.[11]

CLINICAL STAGING

Clinical staging is a valuable part of lymphoma classification. It is well established that lymphoma has a wide-ranging clinical presentation and variable disease progression in many species. This is best described in dogs and cats, in which the anatomic location of lymphoma is extremely variable but is very useful in predicting the clinical course and outcome of the disease. For example, it is generally believed that dogs presenting with lymphoma isolated to the gastrointestinal tract, central nervous system, or other non-nodal visceral sites have a worse prognosis than dogs with a strictly nodal form of lymphoma.[12] The same location effect likely applies to ferrets with lymphoma. Consequently, complete clinical staging is recommended for all ferrets upon diagnosis of lymphoma to determine the degree of illness affecting the patient.

The ideal workup for a staging process consists of a complete blood cell count (CBC), a biochemistry profile, urinalysis, whole-body radiographs (2 views), abdominal ultrasound, and bone marrow aspiration. Whereas most studies in the veterinary literature describe 4 stages of ferret lymphoma, we propose the use of the 5-stage system described below. This staging scheme is similar to that used in dogs and cats and is known to provide valuable prognostic information in those species.[12]

PROPOSED STAGING SCHEME

With the proposed staging scheme, the anatomic site is defined as follows:

A: generalized
B: alimentary
C: thymic
D: skin