Proceedings of the 36th World Small Animal Veterinary Congress
WSAVA
Oct. 14 - 17, 2011
Jeju, Korea

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DIAGNOSIS AND TREATMENT OF FELINE ALIMENTARY LYMPHOMAS

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Abstract

Any old cat with weight loss and chronic gastrointestinal signs should be evaluated thoroughly for systemic illnesses including alimentary lymphoma. Today we see more alimentary form lymphomas in cats than we saw before because of decreased incidences of FeLV infection and anterior mediastinal lymphomas, and probably because we see more aged cats in the clinics. Feline alimentary lymphomas, mostly seen in FeLV-negative aged cats, basically have two distinct types including high-grade lymphomas and low-grade lymphomas, and furthermore it is possible to consider the third category, LGL lymphomas. Diagnosis of high-grade and LGL types is usually straightforward by using FNA cytology or histopathology, while that of low-grade type is usually a challenge. Standard therapies for a high-grade type include surgical resection of the affected intestinal areas and combination chemotherapy with a relatively good response and a prolonged survival time. Low-grade lymphomas can also be treated successfully with a mild type chemotherapy using prednisolone and chlorambucil with long survival times, while the treatments for LGL lymphomas again are the challenge to veterinarians.

Feline lymphomas

One third of feline neoplasms arise from the hematopoietic system, and 50 to 90% of these hematopoietic neoplasms are lymphomas. Thus, lymphomas are the most frequent neoplasm in the cat, with an estimated annual incidence of 200 cases per 100,000 cats. These statements were published quite a long time ago, but it may be still true that lymphomas are the most frequently encountered malignancy in this species. In old days, because of prevalence of feline leukemia virus (FeLV) infection, a great number of lymphoma cases were diagnosed in young cats, and also at that time there were another group of old cats developing lymphomas.

In the recent years, however, the incidence of FeLV infection in the household cats decreased significantly, and the incidence of FeLV-positive anterior mediastinal or multicentric forms of lymphoma in young cats decreased accordingly.

The anatomical classification of feline lymphomas include, anterior mediastinal, multicentric, alimentary,
central nervous system (CNS), cutaneous, and solitary renal. Acute lymphoblastic leukemia (ALL), again with a high FeLV-positive incidence in young cats, may be included in this classification, but it is relatively rare as compared to lymphomas.

**Alimentary lymphomas**

Probably due to an increased number of FeLV-negative old cats, the alimentary form lymphomas are more frequently diagnosed. In the 1970’s survey, the alimentary form comprised only 15% of feline lymphomas, while more recent 1998 study demonstrated that they comprise 34% of all lymphomas. In the author’s hospital in Tokyo, Japan, in the recent years, among 43 cases of microscopically confirmed feline lymphoma cases, 51% were the alimentary form, while FeLV positive anterior mediastinal form accounted for 16%. The median or average age of the cats with alimentary lymphomas is around 10 years old, and they are mostly FeLV negative. There are a few papers reporting association of feline immunodeficiency virus (FIV) infection and feline lymphomas.

Alimentary lymphomas include a gastrointestinal (GI) form, a mesentery lymph node form, and a hepatic form. The macroscopic lesions for the GI form are solitary or multiple mass-forming in the GI tract, and diffuse thickening of the GI tract. The gastric form is rare, but the clinical presentation is chronic vomiting and thickening of the gastric wall. The mass formation in the intestine is seen in the small intestine, iliocecal junction, and colon. The mesentery lymph node form is characterized by enlarged lymph nodes with or without involvement of the intestines. The hepatic form is either diffuse involvement or multiple mass formations in the liver.

Depending on the proliferating cell type, they are classified into high-grade or low-grade. Also there is a special group of lymphoma consisting of neoplastic large granular lymphocytes (LGL).

The clinical presentations are variable, but any old cats with chronic GI signs (vomiting and diarrhea) with weight loss or other signs of illness such as loss of appetite should be evaluated for lymphoma.

**How are they diagnosed?**

For old cats with weight loss, with or without GI signs, initial screening tests are focused on ruling out liver disease, diabetes mellitus, chronic kidney disease and hyperthyroidism. For those losing appetite, a pancreatic enzyme test, Spec-fPL should be ordered to rule out pancreatitis. Plain X-ray and abdominal ultrasound are helpful detecting masses. High-grade type is usually associated with destruction of GI structures, and mass formation and loss of prominent layers in the intestine are usually apparent. In some low-grade type, ultrasound findings are subtle, but thickening of one or some layers in the intestine may be noted. The thickening of the intestinal wall and lymphadenopathy, however, are also seen with IBD with very similar symptoms.

Any mass or lymphadenopathy can be approached by fine needle biopsy and cytology. The diagnosis of high-grade lymphoma is possible if the percentage of the blast cells exceed 50% of the total nucleated cells. In the case of low-grade lymphoma, a uniform population of mature small lymphocyte with no evidence of inflammation or hyperplasia may lead to a strong suspicion of a low-grade lymphoma, but histopathologic confirmation is always necessary. Even with HE-stained histopathology alone, it is sometimes difficult to make a definitive diagnosis. Immunochemical staining or PCR may be used as an adjunct, but they do not give a final answer. For histopathologic diagnosis, it is best to obtain multiple full-thickness biopsies of the intestine and a wedge type biopsy of the node. In reality, however, the cat owners often are reluctant to have laparotomy. It is important to remember that the endoscopic biopsy oftentimes may miss the mucosal lesion, or lesions in the...
submucosa and the muscular layer.

The LGL type lymphomas are characterized by the presence of cytoplasmic azurophilic granules in the neoplastic lymphocytes. The nuclear morphology may indicate either high-grade or low-grade, but in general they cause severe necrosis of the tissue involved and are considered to have aggressive behaviors.

The distinction between T cells and B cells is not clinically important. Rather, the distinction between high-grade versus low-grade is very important. However, recognition of LGL lymphomas is very important, since most carry poor prognosis.

**How are they treated?**

High-grade lymphomas are generally treated with COP based combination chemotherapies. Prior to the chemotherapy, surgical resection of the intestinal masses is generally recommended to prevent necrosis and perforation of the intestine and resultant bacterial peritonitis. Surgery is not indicated for hepatic or nodal high-grade lymphomas.

For COP based chemotherapy, doxorubixcin is usually added. Also, L-asparaginase (L-Asp) can be added. The complete remission (CR) with the COP based chemotherapies is reportedly 30 to 64%, with median survival of 4-8.2 months. In NCSU COP based chemotherapy, L-Asp is used once in the beginning of the therapy at 400U/kg sc (Week 0), vincristine at 0.025 mg/kg iv every 2 weeks (Weeks 0, 2, 4, 6, 8), cyclophosphamide at 10 mg/kg iv at Week 1 and Week 5, methotrexate at 0.8 mg/kg iv at Week 3, doxorubicin 25mg/m2 iv at Week 7, and prednisolone 5 mg/cat bid-sid po for the entire 8 weeks. Another COP based combination chemotherapy is COPLA, with initial 2 doses of L-ASP and later 3 doses of doxorubicin and COP protocol in between. There are several dosage regimens for doxorubicin in cats, and they vary greatly in the drug dosage. The NCSU protocol uses 20 mg/m2 which is the highest dosage such as a 4-kg cat receives 6.25 mg. The 1mg/kg protocol is 4 mg for a 4-kg cat, and the 20 mg/ m2 is 5mg for a 4-kg cat. It seems that the maximum cumulative dosage is 150 mg/ m2 in cats. In a recurrent case, the use of CCNU at 50-60 mg/m2 po every 6 weeks can be considered.

Currently, the same therapies are applied for LGL lymphomas, but survival time is very short. One type of LGL with very large cytoplasmic granules are gamma-delta TCR T lymphocytes, and the granules contain potent cytotoxic protein called perforin. These LGL lymphomas only respond partially to COPLA or CCNU protocols.

Low-grade lymphomas are best treated with prednisone (or prednisolone) and chlorambucil. There are studies using a high dose intensity chlorambucil at 15 mg/m2 po for 4 days, repeated every 3 weeks, and 3 mg/ kg or 10 mg/cat prednisone sid, with CR of 69-76 % and median CR duration of approximately 20 months. Prednisone must be metabolized in the cat liver to give prednisolone, but there is almost no difference in the potency if the liver function is normal. However, it may be possible to use a lower dose if prednisolone is used. There are other dosing regimens for chlorambucil using a lower dose, and the therapeutic results looks similar for feline low-grade lymphomas. Chlorambucil at 2 mg/cat po every 48 hours plus daily prednisolone at 5-10mg/cat is reported to have similar effect with a CR of 56 %, and the author is currently using this lower dose protocol.