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Advances in the treatment of the cat with lymphoma in practice

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Lymphoma (malignant lymphoma, lymphosarcoma, LSA) is defined as a lymphoid malignancy that originates from solid organs (eg, lymph nodes, liver, spleen). This differentiates lymphomas from lymphoid leukaemias, which originate in the bone marrow.

Etiology and epidemiology

Previous reports document that approximately 70% of cats with lymphoma are feline leukaemia virus (FeLV)-positive. The prevalence of viraemia in cats with lymphoma varies with the anatomical form of presentation but, in general, young cats with lymphoma are FeLV-positive, whereas older cats are FeLV-negative. Over the past few years, the prevalence of FeLV infection in cats with lymphoma in our clinic is decreasing. Feline immunodeficiency virus (FIV) infection significantly increases the risk of developing lymphoma.

The age of presentation in cats with lymphoma is bimodal; the first peak occurs at approximately 2 years of age and the second one at approximately 10–12 years of age. The first peak is composed mainly of FeLV-positive cats, whereas the second one includes predominantly FeLV-negative cats. The mean age of presentation of lymphoma in FeLV-positive cats is 3 years, whereas in FeLV-negative cats it is 7–8 years.

Clinical features

Four anatomic forms of presentation are recognised in cats and dogs with lymphoma:

1. Multicentric, characterised by generalised lymphadenopathy, hepatic, splenic, and/or bone marrow involvement;
2. Mediastinal, characterised by mediastinal lymphadenopathy, with or without bone marrow infiltration;
3. Alimentary, characterised by solitary, diffuse, or multifocal gastrointestinal tract infiltration, with or without intra-abdominal lymphadenopathy;
4. Extranodal, affects any organ or tissue (eg, renal, neural, ocular, cutaneous).

In the cat the mediastinal and alimentary forms are more common than the multicentric and extranodal forms. In our clinics, alimentary lymphoma occurs in over half of the cats with this neoplasm.

The clinical findings in cats with lymphoma are related to the anatomic form of presentation. Patients with the generalised or multicentric form are presented with vague, non-specific clinical signs; occasionally the owners detect one or more subcutaneous masses (ie, enlarged lymph nodes) during grooming, and they seek veterinary care. More often, patients are examined because of non-specific clinical signs such as weight loss, anorexia and lethargy. If the enlarged lymph nodes cause mechanical obstruction of lymph drainage, oedema occurs; if they cause compression of the airway, coughing is a presenting complaint.

Physical examination of cats with multicentric lymphoma usually reveals massive generalised lymphadenopathy, with or without

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hepatomegaly, splenomegaly, or extranodal lesions (eg, ocular, cutaneous, renal, neural). The affected lymph nodes are markedly enlarged (5–15 times their normal size), painless and freely movable. A syndrome of idiopathic reactive (hyperplastic) lymphadenopathy can mimic the clinicopathologic features of multicentric lymphoma in cats.

Cats with mediastinal lymphoma are typically young and FeLV-positive, and present for evaluation of dyspnea, coughing or regurgitation of recent onset. Although common in dogs, paraneoplastic hypercalcemia is extremely rare in cats with lymphoma. The respiratory and upper digestive signs are caused by compression from enlarged anterior mediastinal lymph nodes, although malignant pleural effusion can contribute to the severity of the respiratory signs. On physical examination, the abnormalities are usually confined to the thoracic cavity and consist of decreased bronchovesicular sounds, displacement of the normal pulmonary sounds to the dorsocaudal thoracic cavity, dull sound on percussion of the ventral thoracic cavity, and a non-compressible mediastinum. Unilateral or bilateral Horner's syndrome may also occur in cats with mediastinal lymphoma.

Cats with alimentary lymphoma usually have gastrointestinal signs such as vomiting, anorexia, diarrhoea and weight loss. Occasionally, signs compatible with intestinal obstruction or peritonitis (caused by rupture of a lymphomatous mass) may occur. Physical examination in these patients is characterised by the presence of intra-abdominal masses (eg, enlarged mesenteric lymph nodes or intestinal masses) and thickened bowel loops (in diffuse small intestinal lymphoma).

The clinical signs and physical examination findings in cats with extranodal lymphoma are extremely variable and depend on the location of the mass(es). In general, the clinical signs are the result of compression or displacement of normal parenchymal cells in the affected organ (eg, azotemia in renal lymphoma, neurologic signs in central nervous system [CNS] lymphoma). Common extranodal forms in cats include nasopharyngeal, ocular, renal, and neural.

Renal lymphoma is relatively common in cats. Cats with this anatomic form are presented for evaluation of vague clinical signs, usually secondary to chronic renal failure. Physical examination reveals an emaciated cat that is usually anaemic and has large, irregular and firm kidneys; both kidneys are commonly affected. There is a purported association between renal and CNS lymphoma in cats, to the point that some clinicians recommend using drugs that achieve high CNS concentrations (ie, cytosine arabinoside) in cats with renal involvement in attempts to prevent secondary CNS dissemination. In our clinic, this association has not been recognised.

Ocular lymphoma is also common in cats, where it can be either primary or secondary to the multicentric form. A variety of signs and lesions may be present in these patients, including photophobia, blepharospasm, epiphora, hyphema, hypopyon, ocular or retroorbital masses, third eyelid infiltration, anterior uveitis, chorioretinal involvement and retinal detachment.

Nasopharyngeal lymphoma is common in cats. Clinical signs are similar to those of cats with other upper respiratory disorder and include sneezing, unilateral or bilateral nasal discharge (from mucopurulent to frankly haemorrhagic), stertorous breathing, exophthalmus and facial deformity; this is one of the most common extranodal lymphomas in cats in our clinic, and it is far more common than intranasal adenocarcinoma.

Cats with neural lymphoma are presented with a variety of neurologic signs. Although CNS signs are more common, peripheral nerve involvement may occur. Three forms of presentation are clinically recognised, including solitary epidural lymphoma, neuropil (intracranial or intraspinal) lymphoma (also referred to as true CNS lymphoma), and peripheral nerve lymphoma. Neurologic signs are usually multifocal, although solitary intracranial or spinal involvement also occurs. Neural lymphomas can be primary (eg, epidural lymphoma), or they may be secondary to the multicentric form. As mentioned above, secondary CNS lymphoma may be common in cats with the renal form.

A variety of differential diagnoses should be considered when evaluating a cat with suspected lymphoma. The clinician should always bear in mind that lymphomas are great imitators, and they can mimic a large number of neoplastic and non-neoplastic disorders.

Haematological and serum biochemical features

A variety of non-specific haematological and serum biochemical abnormalities can be detected

in cats with lymphoma. The haematologic abnormalities result from bone marrow infiltration with neoplastic cells, splenic hypofunction or hyperfunction (caused by neoplastic infiltrates), chronic disease, or paraneoplastic immune-mediated abnormalities (ie, immune haemolytic anemia or thrombocytopenia—this is rare in cats).

Specific haematologic abnormalities (ie, monocytosis, leukaemoid reactions, eosinophilia) may be caused by the local or systemic production of bioactive substances by the tumour cells (eg, haematopoietic growth factors, interleukins). The serum biochemical abnormalities result from either production of bioactive substances by the tumour cells (ie, paraneoplasia) or from organ failure secondary to neoplastic infiltration. In general, the CBC and profile are rarely diagnostic in cats and dogs with lymphoma.

Radiographic and ultrasonographic features

Radiographic abnormalities in cats with lymphoma vary with the anatomic forms, and in general are secondary to lymphadenopathy or organomegaly (ie, hepatomegaly, splenomegaly, renomegaly). Occasionally, infiltration of other organs (eg, lungs) may lead to the appearance of additional radiographic abnormalities. In cats with mediastinal lymphoma, radiographic changes are usually limited to the presence of an anterior (or, more rarely, posterior) mediastinal mass, with or without pleural effusion.

Grey-scale ultrasound provides an invaluable tool for evaluating suspected or confirmed intra-abdominal lymphoma in cats; this technique is also beneficial when evaluating mediastinal masses. Using this technique, changes in the echogenicity of parenchymal organs (ie, liver, spleen, kidneys) are usually reflective of changes in organ texture secondary to neoplastic infiltration. In addition, enlarged lymphoid structures or organs can easily be identified and aspirated or biopsied.

Several ultrasonographic abnormalities are common in cats with intra-abdominal lymphoma, including hepatomegaly, splenomegaly, changes in the echogenicity of liver and/or spleen (mixed echogenicity or multiple hypoechoic areas), lymphadenopathy, splenic masses and effusion. In a recent study of 11 cats with alimentary lymphoma evaluated ultrasonographically in our clinic, we found hypoechoic masses of the gastric or intestinal wall, focal or diffuse gastric wall thickening, symmetric thickening of the intestinal wall, loss of the normal layered appearance of the gastrointestinal wall, and abdominal lymphadenopathy.

Diagnosis

The clinical features described in preceding paragraphs usually suggest lymphoma; however, before instituting therapy, a confirmatory cytological or histopathological diagnosis should be obtained. In addition, a minimum database consisting of a CBC, serum biochemistry profile and urinalysis should be obtained if the owners are contemplating treatment.

In most cats with multicentric, superficial extranodal, mediastinal, or alimentary lymphoma, a diagnosis can easily be obtained by fine-needle aspiration cytology of the affected organ(s) or lymph node(s).

In our practice, lymphomas can be diagnosed cytologically in approximately 70–75% of cats evaluated (ie, usually in only 25% to 30% of the cats is histopathologic evaluation of a surgically excised lymph node necessary to establish a diagnosis). Until conclusive evidence that the histopathologic classification of feline lymphomas offers prognostic information, the surgical removal of a lymph node or extranodal mass for histopathologic evaluation in a patient with a cytologic diagnosis of lymphoma is not indicated.

I recommend evaluating at least a CBC, a serum biochemistry profile and a urinalysis in all cats with lymphoma in which owners are contemplating therapy. In addition, a FeLV and an FIV test should be obtained in cats. This minimum database can provide a wealth of information that can assist the owner (and the clinician) in deciding whether or not to treat the patient. In addition, once a decision to treat the patient has been made, the clinicopathologic abnormalities (or the lack thereof) usually dictate which treatment(s) to use. For example, in a cat with pronounced cytopaenias caused by lymphomatous infiltration of the bone marrow, a highly myelosuppressive chemotherapy combination will almost certainly result in severe neutropaenia, and it should therefore be avoided.

In cats with lymphoma of the neuropil, cerebrospinal fluid (CSF) analysis may be diagnostic, containing high numbers of neoplastic lymphoid cells and an increased protein concentration. The diagnosis of extradural masses

usually requires collection of a surgical specimen for cytological or histopathological evaluation.

Treatment

Once a cytological or histopathological diagnosis of lymphoma is established, the prognosis and potential therapeutic options are usually discussed with the cat's owner. Remission rates in cats with lymphoma treated with various chemotherapy protocols are approximately 65–75%. Most cats with lymphoma are expected to live 6–9 months when treated with multiple agent chemotherapy protocols, with or without surgery and/or radiotherapy; approximately 20% of the cats live in excess of 1 year. In FeLV-positive cats the prognosis is worse (survival rate of 3–4 months), whereas in FeLV-negative cats, survival times are longer (9–18 months, depending on the anatomical form). The approximate survival time for untreated cats with lymphoma is 4–8 weeks. Probably the most important reasons why survival times are shorter in cats than in dogs with lymphoma is that remissions are difficult to reinduce once the tumour has relapsed.

It is my experience that, even when a cat is presented with stage I extranodal lymphoma, systemic dissemination of the disease usually occurs weeks to months after diagnosis. Therefore the mainstay of treatment for cats with lymphoma is chemotherapy, given the fact that lymphomas are (or will eventually be) systemic neoplasms. Surgery and/or radiotherapy can be used to treat localised lymphomas before or during chemotherapy. In this section general guidelines for the management of patients with lymphoma are presented. The protocols recommended in this article have been used in our clinic with a success rate comparable to that of other treatments published in the literature.

The treatment of cats with lymphoma is divided into several phases or strategies: induction of remission, intensification, maintenance, and reinduction of remission or 'rescue' (Table 1). Immediately after diagnosis, a relatively aggressive multiple agent chemotherapy protocol (COAP) is used to induce remission; during this phase, which lasts 6–8 weeks, the patient is evaluated by a veterinarian weekly, at which time they receive an intravenous injection of an antimitotic agent (vincristine) in addition to undergoing a routine physical examination (with or without a CBC). If at the end of this phase the patient is considered to be in complete remission (CR; ie, complete disappearance of all neoplastic masses), the maintenance phase is initiated. During the maintenance phase, a multiple agent chemotherapy protocol consisting of three drugs (LMP) administered orally is used, so that the patient requires less intensive monitoring (once every 6–8 weeks). This phase continues until the tumour relapses (ie, the patient is out of remission), at which time the reinduction phase begins. This phase is similar to the induction phase, in that intensive treatments are used. Once remission is obtained, the patient is placed again on a maintenance protocol that is usually a modification of the original maintenance protocols (at OSU we typically use the LMP protocol, but we substitute Cytosar for the methotrexate, at a dose of 200–300 mg/m2, SQ, every other week). If at the end of the induction phase the patient is not in CR, intensification with L-asparaginase is recommended before initiating the maintenance phase. In addition to the chemotherapeutic approach discussed in this section, a variety of protocols have been used successfully in the treatment of cats with lymphoma.

Management of cats with solitary or extranodal lymphomas

A problem arises when the clinician is facing a patient with a solitary lymphoma, regardless of whether it is nodal (ie, a stage IA patient) or extranodal (ie, a solitary cutaneous mass). Should this mass (or lymph node) be treated as any other solitary malignancies are treated (ie, by wide surgical excision)? Should the patient be treated primarily with chemotherapy? Should the cat be treated with a combination of surgery, radiation and chemotherapy? Unfortunately, there are no correct answers to these questions.

As discussed above, it has been my experience that solitary lymphomas eventually become systemic in most patients. Although cures have been obtained after surgically excising or irradiating solitary lymphomas, they are extremely rare. Therefore, our approach is not to underestimate this neoplasm by treating the patient with only a local modality of treatment such as surgery or radiotherapy. The following guidelines can be used when dealing with this subset of patients:

1. If the tumour is easily resectable (eg, cutaneous mass, superficial lymph node, intraocular mass) and the surgical procedure does not pose a significant risk to the patient,

Table 1. Chemotherapy protocols used for the treatment of cats with lymphoma at The Ohio State University Veterinary Teaching Hospital

Induction of remission
COAP protocol (Use for 6–10 weeks, then use LMP)
cyclophosphamide (Cytoxan©) 200–300 mg/m^2, PO, every 3 weeks
vincristine (Oncovin©) 0.5 mg/m^{2}BSA, IV, once a week
cytosine arabinoside (Cytosar-U©) 100 mg/m^{2}BSA/day, IV drip or SQ, for 2 days (Note: *cytosine arabinoside may cause pain or discomfort upon subcutaneous injection in cats*)
prednisone 50 mg/m^{2}BSA, PO, sid for a week; then 20 mg/m^{2}BSA PO, every other day

Intensification
doxorubicin (Adriamycin©) 25 mg/m^2, IV, every 3 weeks or
mitoxantrone (Novantrone©) 4–6 mg/m^2, IV, every 3 weeks

Maintenance (Use until relapse occurs; then go to 'rescue')
LMP protocol
chlorambucil (Leukeran©) 20 mg/m^{2}BSA, PO, every other week
methotrexate (Methotrexate©) 2.5 mg/m^{2}BSA, PO, 2–3 times per week
prednisone 20 mg/m^2, PO, every other day
COAP protocol
use as above every other week for six treatments, then every third week for additional six treatments, and try to maintain the patient on one treatment every 4th week.

Maintenance therapy is continued until the tumour relapses

Rescue
MiC protocol (21 day cycle)
mitoxantrone (Novantrone©) 4–6 mg/m^2, IV drip over 4–6 h on day 1
cyclophosphamide (Cytoxan©) 200–300 mg/m^2, PO, day 15 or 16
AC protocol (21 day cycle)
doxorubicin (Adriamycin©) 25 mg/m^2, IV, on day 1
cyclophosphamide (Cytoxan©) 200–300 mg/m^2, PO, day 15 or 16
MiCA protocol (21 day cycle)
mitoxantrone (Novantrone©) 4–5 mg/m^2, IV drip over 4–6 h on day 1
cyclophosphamide (Cytoxan©) 200–300 mg/m^2, PO, day 15 or 16
cytosine arabinoside (Cytosar-u©) 200 mg/m^2, IV drip over 4–6 h (Mixed in the same bag with mitoxantrone) on day 1
CHOP protocol (21 day cycle)
cyclophosphamide (Cytoxan©) 200–300 mg/m^2, IV, on day 10
doxorubicin (Adriamycin©) 20–25 mg/m^2, IV, on day 1
vincristine (Oncovin©) 0.5 mg/m^2, IV, on days 8 and 15
prednisone 20–25 mg/m^2, PO, every other day

the mass should be resected and evaluated histopathologically, and the patient treated with chemotherapy;
2. If the mass is difficult or impossible to resect or if a major surgical procedure would pose undue risk for the patient, a fine-needle aspirate or needle biopsy of the mass should be obtained, and the patient should be treated with chemotherapy (with or without radiotherapy of the incompletely excised primary lesion).

Radiotherapy constitutes an excellent treatment modality for patients with solitary lymphomas. Lymphoma cells are radiosensitive and marked responses (CR or PR) are seen within hours or days of initiating such treatment. Different sources and protocols have been used in cats with lymphoma but, in general, they result in the delivery of 3–5 grey (300 to 500 rad) per fraction, for a total of 6–10 fractions (total dose of 30–50 Gy or 3000–5000 rad). As discussed previously, this approach can be used in conjunction with chemotherapy. Special situations in which radiotherapy is also beneficial include CNS lymphomas and upper airway lymphomas leading to respiratory compromise.

Another question that must be answered is if chemotherapy is used, which protocol should be used, and for how long should the patient be treated? This is also a question with no certain answer. Our approach is to use a standard induction chemotherapy protocol (COAP) for most cats with solitary lymphoma, following surgical excision or irradiation; after completion of the induction phase, the patients are treated with a maintenance protocol (LMP), and remission is reinduced as necessary (as in other forms of lymphoma). In our experience, the use of maintenance chemotherapy protocols alone after surgical excision of solitary lymphomas is associated with early relapse in most patients.