

Canine Lymphoma

Holly H. Crain

Mississippi State University

Advisor: Dr. Taya Marquardt

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Introduction

Lymphoma is the most common hematopoietic malignancy in the dog and is generally seen in middle-aged to older dogs and historically medium to large breeds (Williams, Zandvliet). The most common form of canine lymphoma is high-grade multicentric generally presenting as lymphadenopathy with or without other nonspecific clinical signs. However, lymphoma can manifest in other organs including the spleen, liver, gastrointestinal tract, and skin. The cause of canine lymphoma is unknown, but there are several speculations including genetic and environmental components (Zandvliet). As a round cell neoplasia, a fine needle aspirate of the affected organ is usually diagnostic. Lymphoma is generally chemotherapy responsive. The CHOP protocol is the preferred chemotherapeutic treatment for canine lymphoma (Burton et al.). Prognosis of lymphoma varies with grade, stage, clinical signs, immunophenotype, and location (Zandvliet).

History and Presentation

Canine lymphoma can present in a variety of ways. Dogs with lymphoma may develop nonspecific clinical signs including lethargy, inappetence, weight loss, vomiting, and diarrhea. Owners may notice a swelling or lump in the area of an enlarged lymph node. At times, signs of lymphoma can be an incidental finding on physical exam or routine bloodwork of an otherwise apparently healthy animal.

Canine lymphoma most commonly occurs in middle-aged to older dogs (Zandvliet). The most common breeds to develop canine lymphoma include Boxer, Bassett Hound, Scottish Terrier, Saint Bernard, Rottweiler, German Shepherd, Golden Retriever, and Bulldog (Kitchell). Male dogs may be slightly overrepresented (Burton et al.).

Pathophysiology

Neoplastic diseases are classified as round cell tumors, sarcomas, or carcinomas. Canine lymphoma is considered a round cell tumor and is the most common hematopoietic malignancy in dogs (Zandvliet). Lymphoma occurs due to malignant transformation of lymphoid tissues resulting in the production and development of malignant lymphocytes. Malignancy can occur in B-lymphocytes, T-lymphocytes, or both. At this time, a specific cause of canine lymphoma is not known, but there may be environmental or genetic sources. The most common origination of canine lymphoma occurs in the lymph nodes and the spleen. Nevertheless, canine lymphoma can arise in any location in the body that contains lymphoid cells.

Lymphoma can be classified further by anatomic location. Multicentric canine lymphoma involving one or multiple lymph nodes is the most common presentation followed by gastrointestinal, cutaneous, mediastinal, and extranodal. Clinical signs in multicentric canine lymphoma include generalized lymphadenopathy along with nonspecific signs. Clinical signs of gastrointestinal lymphoma include lethargy, inappetence, vomiting, and diarrhea. Cutaneous lymphoma can present with plaques, papules, or ulcers.

Histopathology of affected tissues is required for grading of canine lymphoma. High-grade is more common than low-grade in dogs. High-grade tumors tend to be more aggressive than low-grade having a higher mitotic index and progressing more rapidly. Because high-grade canine lymphoma is more biologically active, it tends to be more responsive to chemotherapeutic treatment. Low-grade tumors still tend to be associated with longer survival times than high-grade tumors even when chemotherapeutic treatment is pursued as the low-grade canine lymphoma disease process is less severe. Low-grade tumors may also have a longer period before illustrating clinical signs (Fan).

Differential Diagnoses

Because the most common clinical presentation of canine lymphoma includes generalized lymphadenopathy, there are several differential diagnoses including infectious causes, allergies, edema, lymph node infarction, or less likely metastatic disease. Infectious causes including fungal disease such as blastomycosis and Rickettsial infection including Rocky Mountain Spotted Fever and Ehrlichiosis must be ruled out as the cause of generalized lymphadenopathy.

Diagnostic Approach and Considerations

Round cell tumor cells tend to exfoliate well making fine needle aspirate of the enlarged lymph node or mass with cytology the diagnostic test of choice (Brodsky et al.). However, histopathology is required for grading of lymphoma based on mitotic figures and nuclear size and morphology (Zandvliet). It is advised to avoid fine needle aspirate or biopsy of submandibular lymph nodes if other lymph nodes are involved as the submandibular lymph nodes may be reactive due to dental disease.

Staging of disease in cases of canine lymphoma is important in characterizing the patient's disease burden and providing a baseline for monitoring response to therapy. Diagnostic tests involved in staging canine lymphoma may include complete blood count, serum chemistry, urinalysis, thoracic and abdominal radiographs, abdominal ultrasound with fine needle aspirates of abnormal organs as well as liver and spleen, lymph node or mass aspirate or biopsy, ophthalmic exam, and bone marrow aspirate or biopsy. There are five stages of canine lymphoma. Stage I is limited to involvement of a single lymph node. Stage II includes involvement of multiple lymph nodes on one side of the diaphragm. Stage III is generalized lymph node involvement. Stage IV occurs when the liver or spleen is involved. Stage V includes

involvement of any tissue outside of the liver, spleen, or lymph nodes, the most common location being the bone marrow (Zandvliet). Substage A indicates that there are no clinical signs involved with canine lymphoma. Substage B means that there are clinical signs at the time of diagnosis (Brodsky et al.).

Prognosis can also be based on immunophenotype which can be determined through special staining of cytology or biopsy samples. The most common antibodies used in these special stains are CD20 and CD21 for B-cell immunophenotype and CD3, CD4, and CD8 for T-cell immunophenotype. An alternative to immunohistochemistry is PCR assay for antigen receptor rearrangement (PARR) which amplifies genes and receptors to determine B-cell or T-cell immunophenotype (Zandvliet). In terms of prognosis, B-cell lymphoma tends to be more responsive to chemotherapy resulting in longer survival and remission times. T-cell lymphoma tends to be less responsive to chemotherapy and yields lower remission rates, shorter remission times, and shorter survival times (Brodsky et al.).

Treatment Options

The treatment of choice in canine lymphoma is combination chemotherapy as lymphoma is a systemic disorder (Alvarez et al.). Surgery and radiation are options if disease is in a single anatomic location (Zandvliet).

The most common and most effective treatment method for multicentric canine lymphoma is CHOP protocol which is a combination chemotherapeutic drug protocol. The CHOP protocol incorporates a rotating schedule of cyclophosphamide, doxorubicin, vincristine, and prednisone. Remission rates reach 90% with a duration of greater than seven months (Alvarez et al., Burton et al.). Side effects and toxicities increase with combination protocols

compared to single-agent protocols. With combination chemotherapy, owners must be fully committed as weekly administration and monitoring of bloodwork and urinalysis are required for the extent of the protocol which can range from 15 to 26 weeks (Burton, Rebhun).

The most common single agent chemotherapeutic drug for canine lymphoma is doxorubicin. Remission rates using only doxorubicin for treatment are around 75% with a duration of up to seven months. Side effects of doxorubicin, like most chemotherapeutic drugs, include myelosuppression and gastrointestinal signs. Doxorubicin is also extremely irritating with extravasation causing sloughing of the tissue around the intravenous catheter site. Even more importantly, cardiac toxicity can occur with doxorubicin acutely or cumulatively with subsequent administrations. Cardiac toxicity can lead to ECG changes followed by cardiac arrest (Chatterjee).

Conservative treatment incorporates a single-agent protocol using prednisone. Remission rates treating with only prednisone are approximately 30-40% with a duration of up to two months. Prednisone works by decreasing the number of lymphocytes in the body by initiating apoptosis of lymphocytes and lymphoblasts. However, using prednisone initially can lead to drug resistance if chemotherapy is started in the future which should be considered before deciding to begin this glucocorticoid therapy (Zandvliet). Side effects of prednisone include immunosuppression, gastrointestinal signs, panting, anxiety, and increased thirst and urination.

The most common cause of treatment failure with neoplastic disease is drug resistance. Drug resistance occurs at the level of the neoplastic cell. During the chemotherapeutic protocol, the first cells to die off in the reduction of disease are the most sensitive to the drugs being used. The cells that survive each round of treatment are the most resistant cells. Eventually the only cells that are left in the neoplastic population are resistant to the drugs being used in the

chemotherapeutic protocol. At that time, the patient has failed the current protocol and rescue therapeutic protocols can be implemented, but response is less likely and remission duration is shorter (Alvarez et al.).

Prognosis

In general, negative prognostic indicators include T-cell immunophenotype, gastrointestinal and cutaneous lymphoma, substage B, hypercalcemia, and previous glucocorticoid administration (Brodsky et al.). The goal of treatment is not to cure the patient of canine lymphoma but to control and manage the disease ensuring the highest possible quality of life for the patient.

Conclusion

In conclusion, canine lymphoma is the most frequently seen hematopoietic malignancy in the dog. The most common form is multicentric lymphoma usually presenting with generalized lymphadenopathy. Other organs can also be affected by lymphoma especially the spleen and liver. At this point, the cause of canine lymphoma has yet to be determined, but genetic and environmental factors are suspected. Classified as a round cell neoplasia, canine lymphoma can often be diagnosed with fine needle aspirate and cytology, but biopsy with histopathology may be required for definitive diagnosis. Prognosis varies with grade, stage, clinical signs, immunophenotype, and location, but canine lymphoma is generally responsive to combination chemotherapeutic protocols.

References

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