Veterinary
Science & Technology

Eubanks, J Veterinar Sci Technolo 2014, 5:4
http://dx.doi.org/10.4172/2157-7579.1000191

Review Article Open Access

Mediastinal Lymphosarcoma in a Seven-Month Old Labrador Retriever

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Abstract

A seven-month-old female spayed Labrador retriever was diagnosed with canine lymphosarcoma. The initial presenting sign was vomiting with a history of possible foreign body ingestion. Laboratory data revealed hypercalcemia and thoracic radiographs demonstrated a mediastinal mass. A diagnosis of mediastinal lymphosarcoma was based on thoracic radiographs and subsequent cytology of the mass. The case was managed with chemotherapy and nutrition. The dog improved for a brief period and was euthanized seven weeks after initial presentation due to disease progression and poor long-term prognosis. This case was unique considering the age of the dog involved.

Keywords: Lymphosarcoma; Hypercalcemia; LSA; Animals

Introduction

The words "canine lymphosarcoma" invoke images of a middle-aged dog with extremely enlarged lymph nodes or a chronic skin or gastrointestinal condition that worsens despite therapy. Similar to non-Hodgkin's lymphoma in humans, canine lymphosarcoma (LSA) is a spontaneous neoplasm resulting from the clonal proliferation of malignant lymphocytes within solid tissues [1]. Lymphosarcoma (also referred to as lymphoma in veterinary literature) is the third most commonly diagnosed malignancy in the canine and accounts for 7% - 24% of all canine neoplasms [1]. Though LSA ranks among the most treatable of all canine neoplasms, many factors contribute to the pathogenesis of the disease and affect the prognosis and outcome of a case. There is relatively little information about LSA in the juvenile canine. This paper presents information about LSA and demonstrates a case that, for several reasons, had a very guarded prognosis.

Possible etiological factors for LSA include viral infections, chromosomal abnormalities, exposure to chemicals such as herbicides, electromagnetic radiation, and genetic predisposition. To date, no definitive cause has been determined [1-4]. Recent information has suggested a potential link between hematopoetic neoplasia such as LSA and autoimmune or immune system disease [1]. In 1992, Keller determined that dogs with immune-mediated thrombocytopenia had a greater occurrence of lymphoma than the general population. Additionally other links between altered immune responses and subsequent development of LSA have been made [1,5].

There are several classification schemes for LSA. Traditionally, LSA has been classified based on anatomic location and is either multicentric (80-85% of cases), alimentary (7%), cutaneous (6%), mediastinal or thymic (3%) or extranodal (central nervous system, spinal and rarely skeletal) [1,3]. The scheme developed by the National Cancer Institute called the Working Formulation (NCI-WF) is useful in classifying dogs and cats with lymphoma and is thus the most commonly accepted classification scheme in veterinary medicine [1,4]. The NCI-WF classifies tumors as low-, intermediate-, or high-grade based on their mitotic indices and natural rate of progression. This is commonly referred to as the "histological grade" of a tumor. A high-grade tumor is one that is populated by large immature lymphoid cells (lymphoblasts) with abundant cytoplasm and high mitotic activity. Low-grade tumors have small lymphoid cells (lymphocytes) with a low mitotic rate. They are more slowly progressive than their high-grade counterparts and are usually B-cell tumors [4].

Dogs with a clinical stage IV or V according to the World Health Organization's Clinical Staging for Tumors of Domestic Animals or those with concurrent systemic signs of disease may have a poorer prognosis than animals with a stage III or below and no systemic signs. Other grading parameters such as AgNOR (agyrophilic nucleolar organizer regions) scores have been shown to have an equivocal influence on prognosis [1].

Case Report

A seven-month old female spayed Labrador retriever weighing 17.73 kg was presented after-hours for occasional vomiting, slight lethargy, and partial anorexia of two days duration. The dog had a history of chewing and ingesting various foreign objects. The dog resided in the southeastern U.S. and had not traveled outside of the region. Toxin exposure was considered unlikely.

On physical exam, the dog was alert and responsive, though she did retch occasionally, but did not vomit. A CBC, serum chemistry profile, and urinalysis were submitted for in-house testing. Results were normal with the exception of increases in serum calcium (12.65 mg/dl; reference range 7.8-12.60 mg/dl), BUN (32.8 mg/dl; reference range 7.0-29.0), and serum creatinine (2.03 mg/dl; reference range 0.3-1.20 mg/dl). The urine specific gravity was 1.006. A direct fecal smear and a Sheather's sugar flotation were performed and were both negative. Plain abdominal films, as well as a barium series, were normal.

Intravenous fluid therapy was begun with 0.9% normal saline at twice maintenance rate (125 ml/hr) with 20 µEq KCl/L. Additionally, sucralfate[a] (0.5 gm q 8 hrs) and cimetidine (75 mg q 8 hrs) were begun, and the dog was kept overnight for observation.

The following morning, a repeat calcium level at an outside laboratory revealed elevated serum calcium (16.6 mg/dl; reference range 8.8-11.20 mg/dl). Because of the suspicion of LSA, a thoracic chest radiograph was taken (Figure 1) which revealed a mediastinal

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Received December 26, 2013; **Accepted** August 28, 2014; **Published** August 30, 2014

Citation: Eubanks DL (2014) Mediastinal Lymphosarcoma in a Seven-Month Old Labrador Retriever. J Veterinar Sci Technol 5: 191. doi:10.4172/2157-7579.1000191

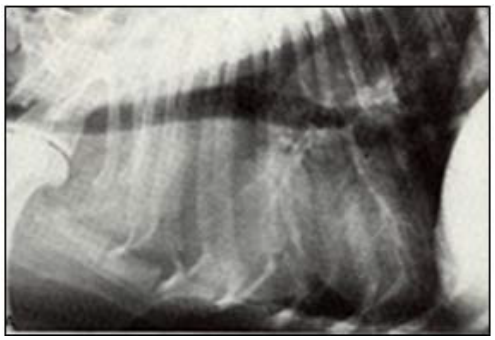

Figure 1: Thoracic Radiograph showing mediastinal mass.

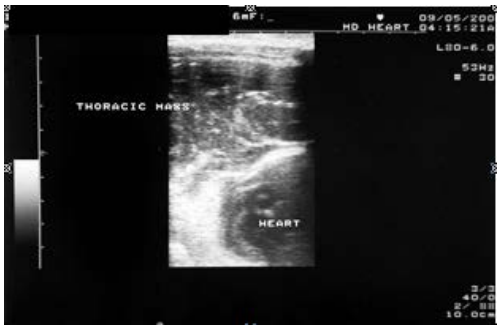

Figure 2: Ultrasound of cranial mediastinal mass.

mass displacing the heart dorsocaudally and to the right, elevating the trachea and compressing the lungs. On ultrasound, a large mass of varying echogenicities with multifocal encapsulated areas of soft tissue was noted (Figure 2).

Based on the location of the mass and the presence of hypercalcemia, a tentative diagnosis of mediastinal lymphosarcoma was made.

Results of a coagulation profile were normal. The dog was sedated with 0.4 mg/kg (7.1 mg) butorphanol and 0.02 mg/kg (0.35 mg) acepromazine, and an ultrasound-guided fine needle aspirate of the mass was performed. Results of the cytology revealed abundant blood and lymphocytes, most of which (approximately 90-95%) were pleomorphic lymphoblasts. The remaining cells were small mature lymphocytes. The lymphoblasts exhibited excess anisocytosis, anisokaryosis, and variation in nucleolar number and size. Numerous lymphoblasts constituted approximately 90% of the cell population on the slide. Only a few mature lymphocytes were observed.

Based on these results and clinical signs, a confirmed diagnosis of lymphoblastic lymphosarcoma was made. The owner declined further diagnostic testing including bone marrow evaluation and immunophenotying. A guarded prognosis was given for long-term survival. The dog was maintained on IV 0.9% saline at twice the maintenance rate (125 ml/hr) with 20 μEq KCl/L, and plans were made to begin chemotherapy the following morning. Chemotherapy was administered according to the following COAP protocol:

50 mg/m^2 (33 mg) Cyclophosphamide[e] was given orally 4 consecutive days per week for the duration of the induction period (which was to be 8 weeks). 0.5 mg/m (0.3 mg) Vincristine sulfate was given IV once weekly for the duration of the induction period. 100 mg/m^2 (66 mg) Cytosine Arabinoside[g] was given SQ for the first 4 days of the induction period only. 50 mg/m^2 (30 mg) Prednisone was given orally once daily for the first week. After the first week, the dose was cut in half and given every other day for the duration of the induction period.

A CBC was performed prior to administration of vincristine each week. If the white blood cell count (WBC) was <3500 cell/μL or if the neutrophil count was <2500 cells/μL, the treatment was delayed. Serum calcium was also monitored periodically during treatment and remained in the normal reference range.

Initially, the dog responded well to chemotherapy. During days 1-3, the dog began to eat and play. By day 4, her activity was nearly normal and her appetite was increased significantly. By day 5, her serum calcium had returned to a normal level and she had not vomited since prior to the initiation of treatment. Weeks 1-4 on chemotherapy were uneventful with the dog returning to a normal playful routine. She was weighed weekly so that adjustments could be made in the dosages as she grew. She was placed on a low carbohydrate, high protein diet.

Two days prior to the scheduled vincristine for week 5, the dog again began to show signs of lethargy which resolved following the 5th dose of vincristine. The owner declined further diagnostics and the possibility of pursuing a different treatment protocol. Three days prior to the scheduled 6th dose of vincristine, the dog was again lethargic and the prednisone dose was then changed to q 24 hours instead of q 48 hours. Forty-eight hours later, the serum calcium was again elevated (14.4 mg/dl). The next day, the scheduled dose of vincristine was administered resulting in mild increase in energy and attitude. Forty-eight hours later, progressively increasing respiratory effort were noted and the owner elected euthanasia.

Discussion

Lymphocytes arise from a common progenitor cell. Through differentiation, they develop into either T-cells or B-cells. Immunophenotyping utilizes monoclonal antibodies to identify lymphoid tumors as either T (20-25% in dogs) or B lymphocytes (70-75%) or non-B/non-T (<5%) [4]. Identification of a tumor as T-cell or B-cell immunophenotype can assist in determining the prognosis of a specific case. Immunophenotyping has proven valuable in predicting duration of first remission, disease-free interval and survival rates [1].

Clinical signs of LSA vary and are usually associated with the anatomic location of the tumor. The specific anatomical form of LSA referred to as mediastinal LSA is characterized by cranial mediastinal lymph node and/or thymic enlargement [3]. The thymus is the central lymphoid organ for maturing T lymphocytes; therefore, the majority of mediastinal LSA are T-cell neoplasms. It was assumed the mass in this case was of T-cell origin because of its location within the mediastinum [3] as well as the presence of hypercalcemia [1], both of which are more commonly associated with the T-cell phenotype.

Clinical signs include those associated with respiratory compromise due to compression of lung lobes, pleural fluid accumulation, or cranial vena cava syndrome characterized by pitting edema of the anterior cervical and facial regions, as well as the thoracic limb area [1,3]. Dogs may cough, experience dyspnea, and lose weight.

Signs occurring at sites distant to primary or secondary tumors are termed "paraneoplastic syndromes". The effects observed may be due to the production of substances by the tumor, depletion of normal substances related to the presence of the tumor, or a host response to the presence of the tumor such as the release of cytokines or growth factors [1]. The most common paraneoplastic syndrome associated with canine LSA is hypercalcemia.

Hypercalcemia caused by neoplasia can occur through either direct invasion of bone, local release of osteolytic factors, or release of bone-resorbing substances that act at distant sites (humoral hypercalcemia) [6]. The hypercalcemia seen with LSA is likely due to a locally acting osteoclastic factor or a humoral mechanism associated with a parathyroid hormone (PTH)-related peptide. This peptide mimics PTH, causing a rise in serum calcium. Hypercalcemia of malignancy occurs in 20% of dogs with LSA [6], is most often observed with tumors exhibiting the T-cell phenotype, and is frequently associated with a mediastinal mass [1].

Vomiting in hypercalcemic animals is usually associated with gastric atony, gastric ulceration, or, in advanced cases, uremia. Hypercalcemia causes decreased excitability of gastrointestinal smooth muscle, resulting in gastric atony. Likewise, decreased skeletal muscle excitability may contribute to generalized weakness [7].

Hypercalcemia of malignancy typically resolves once the underlying problem has been treated. Medical management such as fluid therapy and furosemide can be instituted. Tumors preferentially metabolize glucose for energy via anaerobic glycolysis, resulting in the formation of excess lactic acid. In 1990, Vail, et al. [8] demonstrated a transient inability to clear increased lactic acid in a group of dogs with lymphoma. Therefore, lactated ringers solution (LRS) should not be used in these patients. Likewise, dextrose-containing solutions have also been associated with hyperlactemia in dogs with LSA [8,9]. If other infectious causes have been ruled out, glucocorticoids can be utilized for their ability to decrease intestinal absorption of calcium and enhance calcium excretion via kidneys. If responsive to glucocorticoids, the probability of the hypercalcemia being due to malignancy rises (steroid response test) [6].

A definitive diagnosis of LSA can be made on histopathological or, sometimes, cytologic evaluation. In multicentric LSA, a fine needle aspirate of an affected lymph node is an easy procedure to perform. In cases of mediastinal LSA, an ultrasound-guided biopsy or aspirate can be obtained. Typical cytology demonstates a monomorphic population of large lymphoblastic cells. Considering that many practitioners rely on cytology alone to diagnose lymphoma, it is important to remember the limitations of cytology when diagnosing lymphocytic (vs lymphoblastic) lymphoma. If cytology of an enlarged lymph node reveals an homogenous population of small lymphocytes with cytologic suggestion of benign hyperplasia, an excisional biopsy or polymerase chain reaction (PCR) should be performed [10]. Histologic evaluation is necessary to determine histologic grade and immunophenotype of the tumor. Clinical signs are often related to tumor location and the presence of paraneoplastic processes.

The prognosis of a dog with LSA depends on several factors including tumor stage, presence or absence of concurrent disease, immunophenotype, histomorphologic grade, and anatomic location of the tumor. Dogs with diffuse alimentary, central nervous system, cutaneous, or intrathoracic forms have decreased survival times [3]. Dogs with T-cell lymphomas typically experience shorter remission/survival times than do those with B-cell tumors [1-3,11]. The presence of concurrent disease supports a negative prognosis. Interestingly, high- and intermediate- grade tumors may respond better to chemotherapy and low-grade tumors may survive longer without aggressive treatment [3,4,11].

Treatment of LSA is based on three general parameters: clinical substage of disease (whether or not animal is ill), histologic grade of tumor, and owner commitment [3]. The average survival of an untreated dog with lymphoma is 4-12 weeks and varies considerably [10]. Chemotherapy utilizing combinations of drugs with differing mechanism of action to achieve maximum result with minimum toxicity is the mainstay of treatment in LSA. Fortunately, chemotherapy drugs are well tolerated by most dogs.

Much of the current information on chemotherapy protocols comes from studies involving a combination of cyclophosphamide, vincristine, and prednisone. Such a protocol has become known as COP (Cytoxan, Oncovin, and prednisone). Overall, there is a 70% clinical response with a median time of remission of 130 days. This protocol is manageable, affordable for most clients, and is associated with a low risk of toxicity and side effects [12,13].

Nutritional management of the cancer patient can prolong survival and remission times, as well as improve the quality of life for a patient. Cancer causes profound alterations in the metabolism of carbohydrates, proteins and fats [7,9,14]. Targeted nutritional support in cancer patients can improve body condition, as well as improve a patient's tolerance for chemotherapeutic medications. Generally, a highly palatable diet low in carbohydrates and high in protein and fat is recommended for small animal cancer patients.

Conclusion

The patient in this case was somewhat unusual due to her age. Little information is available in the literature concerning juvenile LSA, therefore, the projected outcome was uncertain. In some cases, a young age has been associated with a less favorable prognosis. Additionally, mediastinal mass, hypercalcemia, and T-cell phenotype are also associated with poor outcomes. It was speculated that this dog had a T-cell tumor and that it was likely an intermediate or high grade tumor. Immunophenotyping and further histological analysis may have aided in the formation of a more accurate prognosis, but most likely would not have improved the long-term outcome.

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