Lymphosarcoma in the Bovine Patient:

A Case Report of Sporadic Lymphosarcoma

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Introduction

Lymphosarcoma is a common neoplasm documented in many species including: humans, horses, cattle, dogs, and cats. In cattle, the terms bovine lymphoma, bovine lymphosarcoma, or bovine leukosis are used interchangeably in the literature to refer to the same or similar sets of conditions. Lymphosarcoma is divided into two broad categories, enzootic and sporadic.[1] The enzootic type, known sometimes as enzootic bovine leukosis (EBL), is the most commonly described neoplasm in adult cattle.[2] EBL is associated with infection with the bovine leukemia virus (BLV) and is most commonly seen in cattle four years of age or older. The sporadic form of lymphosarcoma, sometimes termed sporadic bovine leukosis (SBL), has three forms, juvenile/calf, thymic/adolescent, and cutaneous. The juvenile/calf form of sporadic bovine leukosis occurs in cattle between three to six months of age with clinical signs of weight loss, anorexia, weakness and lymphadenopathy. Cattle with thymic/adolescent lymphoma can develop masses in the neck region and enlargement of the brisket with pitting edema between six months and two years of age. Clinical signs include dysphagia, dyspnea, tachycardia, or respiratory distress. The third form, cutaneous lymphosarcoma, is diagnosed in cattle between one and three years of age and is characterized by tumor development under the skin. These tumors ulcerate and become necrotic as they grow. None of these three forms of lymphosarcoma are associated with viral infection.[1,2]

History and Presentation:

White Calf was an approximately 10-month-old Braford heifer with a history submandibular and thoracic inlet swelling. Prior to the development of the swelling, she developed clinical signs consistent with bovine respiratory disease (BRD) and was treated with ceftiofur subcutaneously (6.6 mg/kg) and florfenicol (40 mg/kg). Herd mates treated for bovine

respiratory disease in the coinciding time frame responded to treatment while white calf's clinical signs persisted. Two weeks after the onset of clinical signs, she was examined by her referring veterinarian. She had an elevated temperature of 105˚F and aspiration of the submandibular swelling only revealed blood contamination. The referring veterinarian suspected calf diphtheria and treated with procaine penicillin (44,000 U/kg) subcutaneously and flunixin meglumine (2mg/kg) intravenously once daily for three days along with a single subcutaneous injection of two milliliters of vitamin B12. This treatment protocol was repeated two weeks later. Five weeks after the initial onset of clinical signs, white calf's temperature remained elevated at 105˚F and in the time prior to presentation at Mississippi State University College of Veterinary Medicine she was treated with multiple classes of antibiotics with only mild improvement of swelling but never complete resolution.

White Calf presented to the MSU-CVM Food Animal Service on February 17, 2017. Upon presentation, White Calf was depressed and mildly dehydrated (5%). Her body condition was four out of nine with a temperature of 101.0 ˚F, heart rate of eighty-eight beats per minute and respiratory rate of twenty-eight breaths per minute. As historically reported, there was a firm approximately eight centimeter by ten centimeter swelling of the submandibular region consistent with submandibular lymph node enlargement. The rest of her lymph nodes were normal on palpation. There was also approximately six centimeter swelling at the thoracic inlet. Ventral edema was present extending from the submandibular swelling to the thoracic inlet. The patients breathing was labored with an inspiratory stertor and auscultation of all lung fields revealed loud referred upper airway noises. The heart was normal upon auscultation.

Based upon age and the presence of swelling consistent with thymic and submandibular lymph node enlargement, thymic lymphosarcoma was the primary differential. The increased

respiratory effort is commonly associated with this condition. While juvenile lymphosarcoma has also been documented to involve the thymus, this is a much less common presentation and lack of generalized lymphadenopathy made this diagnosis less likely. Due to the fatal nature of sporadic lymphosarcoma, the owner elected for humane euthanasia. Prior to euthanasia, blood was collected to test for bovine leukemia virus.

Pathology

On gross necropsy, marked swelling was present in the caudal mandible and cranial neck region due to enlargement of thymic tissue and lymph nodes in the region. Lymph nodes of the jaw, ventral neck, and mediastinum were all severely enlarged. On cross-section lymph nodes were white to tan in color and bulging. They were soft and homogenous and multiple nodes had infarctions with perinodal fibrosis and rims of hemorrhage. The parietal pleura was thickened with white to tan tissues infiltrating the pleura that expanded the space between the musculature and pleura by up to a centimeter. There were also neoplastic tissues in both the right cranial and middle lung lobes. The liver also had multiple two to five cm white to tan nodules through all lobes infiltrating the portal and central veins.[3]

Histopathological sectioning of the lymph nodes and thymus showed a round cell neoplasm that was densely cellular and consistent with T-cell lymphosarcoma. The lung histopathology showed multifocal areas of similar neoplasm that infiltrated the interstitium and pleura. Marked atelectasis was also present. Liver samples also showed multifocal areas of this same neoplasm infiltrating portal areas and vessel walls.[3]

Pathophysiology

Bovine lymphosarcoma can be divided into two broad categories, the sporadic form which is also known as sporadic bovine leukosis (SBL) and the enzootic form which is also known as enzootic bovine leukosis (EBL) or adult onset lymphoma. Sporadic lymphosarcoma is further subdivided into multiple forms. None of these forms have any known cause and there is no known breed or sex predilections.[1] The forms include calf/juvenile form, the thymic/adolescent form, the cutaneous form, and the atypical form. All sporadic forms of lymphoma are extremely rare. The calf or juvenile form is seen most commonly in calves from the ages of three to six months. However, it has been reported in as wide an age range as one month to three years of age. Clinical signs included weight loss, weakness, and lymphadenopathy. Lymph node enlargement is generalized throughout the body in most cases. Other less common clinical signs include fever, ataxia, diarrhea, or ruminal tympany.[2] Bloodwork results most commonly show lymphocytosis and anemia.[4] This disease is rapidly progressive and has been documented to involve numerous organs not limited to the heart, spleen, liver, and thymus. However, thymic involvement is not as common in this form of lymphoma. This condition is usually fatal within eight weeks of onset.[2]

Thymic lymphoma, also known as adolescent lymphoma is extremely rare and most commonly occurs in cattle between six months and two years of age. Clinical signs include a mass in the neck region with enlargement of the brisket and pitting edema. Other clinical signs include weight loss, dysphagia, rumen tympany, dyspnea, tachycardia, and coughing. Generalized lymphadenopathy is not common with this form of lymphosarcoma, however, superficial cervical and prescapular lymph nodes may both be enlarged. Anemia and lymphocytosis are rare with this condition. Time from recognition of the condition to death ranges from two to nine weeks.[1,2]

Cutaneous lymphoma is unique when compared to the other categories of sporadic lymphoma as it is not as age specific. It has been documented in cattle between one and three years of age. Tumors develop under the surface of the skin in this condition and can become ulcerated and necrotic. Both anemia and atypical lymphocytes are common bloodwork abnormalities with this form. These tumors can either resolve or metastasize to other internal organs such as the lungs or abomasum. It is this metastasis that leads to this form of lymphosarcoma becoming fatal.[4]

There is also a fourth pseudo category of sporadic bovine leukosis which is known as the atypical forms. This category refers to forms that do not fit into other categories. These include case reports of lymphosarcoma impacting the trachea, pericardium, and thigh muscles.[2]

All categories of sporadic bovine leukosis generally occur in young cattle that are bovine leukemia virus (BLV) negative. However, there are new studies that imply that the relationship between bovine leukemia virus infection status and type of lymphosarcoma may not be as well defined. In one case report, there was a heifer seropositive for BLV diagnosed with thymic lymphoma. In this case, proviral DNA was detected within the tumor which supports that thymic lymphosarcoma could potentially be related to bovine leukemia virus infection.[5] However, more cases and research are needed to determine the extent of the relationship between BLV and thymic lymphoma.

Most commonly the adult form of bovine lymphosarcoma which is also known as enzootic bovine lymphosarcoma (EBL) is associated with the bovine leukemia virus. While EBL has been reported in cattle as young as two years of age, it is most commonly diagnosed between four and eight years of age.[5] There is no sex or breed predilection known. While not fully known if genetics influence development of lymphosarcoma in bovine leukemia virus (BLV) positive

cattle, susceptibility to infection with BLV is a highly heritable trait. Studies have shown a heritability of up to 0.48 for the susceptibility to BLV. There is a specific allele type known as bovine major histocompatibility complex (BoLA) that can either provide resistance or increase susceptibility to infection with the virus.[6]

Bovine leukemia virus is spread through many means. The primary method of spread is thought to be through horizontal transmission from contaminated blood containing infected lymphocytes. Routine procedures that allow for the exchange of blood on instruments such as dehorning, vaccination, and castrations could lead to transmission of the disease. Gouge dehorning has specifically been shown to increase the risk of BLV spread. Vertical transmission also has been documented, however, studies show that the percentage of calves that were born to infected mothers and tested positive was very low (4-8%).[6]

In the United States of America, reports on infection rates with bovine leukemia virus (BLV) vary. Dairy herds are most commonly impacted by BLV with over 83% of dairy herds having BLV positive cows. These positive herds are reported to have infection rates exceeding 30% of the herd population.[7] A 2017 study looking at seroprevalence using brucellosis blood samples from animals going to slaughter showed an average seroprevalence of 38.6%. This percentage varied based upon region with the northeast being the highest at 54.3%. Slaughter facilities that processed more dairy cattle had higher rates of infection than those that primarily processed beef cattle.[8]

There are three stages of enzootic bovine leukosis. The first of these is the asymptomatic stage with which the only sign is a positive test for bovine leukemia virus (BLV). The second stage is the persistent lymphocytosis stage. Though studies vary, approximately 30% of cattle

infected with BLV will develop to this stage. The reported percentages of cattle with BLV that will develop lymphoma (third stage) is a wide range between 0.1-10%.[7]

Diagnostic Approach/Considerations

The diagnosis of bovine lymphosarcoma can be difficult as symptoms can be vague and vary greatly based upon the body system impacted by the disease. Most commonly, cattle with lymphosarcoma are admitted with nonspecific signs such as weight loss, fever, or anorexia. In these cases, differentials often include but are not limited to traumatic reticulo-peritonitis, abscesses, lymphosarcoma, or displaced abomasum.[9] For cattle with swellings consistent with possible tumors, other differentials for the swellings include inflammation, abscesses, hematomas, or edema. While lymphosarcoma is often strongly suspected with physical examination and palpation, definitive diagnosis requires further diagnostics.[10] Studies looking at the sensitivity of different antemortem diagnostic methods showed that the top three sensitive tests were surgical exploration with biopsy, lymph node wedge biopsy, and percutaneous aspirate or biopsy.[9] While these tests are relatively straight forward to perform they can be costly to the producer. For this reason, testing is often delayed or not performed and diagnosis often occurs postmortem.

While the diagnosis of bovine lymphosarcoma can be challenging, testing for bovine leukemia virus is relatively simple. There are four serological assays for testing for bovine retroviruses. These include agar gel immunodiffusion (AGID), an enzyme linked immunosorbent assay (ELISA-Ab), western blot (WB) and indirect fluorescent antibody (IFA). Some of these are primarily used in laboratory settings while others are more readily available for commercial usage.[11] The standard tests used most commonly are either the AGID or the ELISA test for the gp-51 antigen.[6] The AGID test is highly specific for the virus but it is less sensitive than other

tests. It can take up to twelve weeks after infection for the virus level to be high enough to be detected by this test. This test also cannot differentiate between natural infection and antibodies received by a calf from colostrum. However, due to the ease of the test and its relatively inexpensive nature, it is still one of the most commonly used tests for commercial herds.[11] The ELISA testing method is generally more sensitive and able to detect a much lower level of the virus. Ninety-five percent of newly infected cattle can be detected by day fifty-five post infection using an ELISA test.[12] However, it is important to remember that a positive BLV test does not guarantee that the patient has or will develop lymphosarcoma.

Treatment and Management

There is currently no viable treatment for either the sporadic or enzootic forms of this condition. While in theory, surgical removal and/or supportive care could be used to alleviate symptoms in some cases, many cases have metastasized at the time of diagnosis and these are not economically feasible options and therefore are not commonly explored. Supportive treatments are primarily used to salvage a valuable fetus or allow time for collection of sperm or embryos from valuable breeding animals.[2] Numerous attempts have been made to develop a vaccination against bovine leukemia virus. However, none of these have been successful thus far. This area of research is ongoing and there are still prototype vaccinations being tested in clinical trials in attempts to find a vaccination.[13]

Due to a lack of vaccinations, the only way that a producer can attempt to reduce the risk of enzootic bovine lymphosarcoma is by controlling the spread of bovine leukemia virus. This can be done by preventing blood transfer between animals by using proper equipment cleaning techniques, new needles with each animal and fly control. As little is known about the sporadic

form of lymphosarcoma, there is little that a producer can do to reduce the risk of its development.

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