

Lymphosarcoma

of the

Equine Species

Carolyn H. Chisholm

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Mississippi State University College of Veterinary Medicine

Advisor:

Micheal Brashier, MS, DVM, ACVIM

Introduction:

What are the odds of your horse developing a devastating cancer? Neoplasia is being diagnosed at rapidly increasing rates, affects all species, and leads to moderately high mortality rates. The most common forms of neoplasia in the equine species are squamous cell carcinoma, melanoma, and lymphosarcoma. Equine hematopoietic neoplasia is categorized into myeloproliferative neoplasias that include myeloid leukemia and malignant histiocytosis, and lymphoproliferative neoplasias that include lymphoid leukemia, lymphoma, and plasma cell or multiple myeloma. Neoplasia only represents a low overall incidence of mortality in the equine species. Lymphosarcoma, also known as lymphoma, is the most common hematopoietic neoplasia that affects the equine species to date, representing approximately 2-3% of all the equine tumors. Equine lymphoma was first reported in the mid-1800s. The disease can occur at any age; however, the most common age range is between 4-10 years. Lymphoma can be differentiated into five different syndromes including multicentric, alimentary, mediastinal, cutaneous, and solitary. The specific clinical signs vary depending on the syndrome and the organs affected. There is no breed or sex predisposition that increases the risk of disease. The disease process of equine lymphoma is very heterogeneous and varies between every animal, which hinders the quick and easy diagnosis that all owners expect upon arrival at a veterinary hospital. The diagnosis of equine lymphoma is typically based on clinical signs, presentation, and the rule out of other metabolic disturbances and diseases. With the delays in initiation of appropriate treatment incurred associated with a diagnosis of exclusion, the patient's health often continues to deteriorate. Euthanasia is unfortunately a common outcome of this disease process due to the advanced stage at which it is typically diagnosed.

History and Presentation:

A patient with equine lymphosarcoma typically presents with nonspecific clinical signs that are the only signs noticed until the disease progresses to end stage, at which point the organs affected begin to show specific signs [2,3,4]. The degree of clinical signs is variable and can depend on the stage, form of disease, and extent of invasion. The most typical history is weight loss, inappetence, and lethargy [1,2,3]. Nonspecific clinical signs may also include, but are not limited to ventral edema, lymphadenopathy, fever, increased pulse and respiration, and hematological changes [1,2].

Multicentric lymphoma is the most common form of equine lymphoma [2]. Clinical signs typically include the nonspecific as previously stated, but could also include abdominal distension, icterus, malabsorption syndrome, hematuria, or polydipsia and polyuria [2]. Neurological signs can also develop and present with ataxia, cranial nerve deficits, Horner's syndrome, fecal and urinary incontinence, and seizures [2]. Clinical signs of alimentary lymphoma are similar to multicentric, but normally do not include neurological signs and tend to be overrepresented in young animals and is sometimes referred to as juvenile lymphosarcoma [2]. Cutaneous lymphoma, which is not as common as the multicentric form, however can manifest with clinical signs of multifocal subcutaneous nodules, alopecia, or ulcerated and exudative skin lesions [2]. Mediastinal lymphoma can display clinical signs of dyspnea, coughing, jugular distention, muffled heart sounds, and possibly pleural fluid [2]. The presenting history and clinical presentation can be nonspecific and make the differential diagnosis list long. Equine lymphoma is not clearly understood at this time period; however, the pathophysiology is being researched.

Pathophysiology:

Lymphosarcoma is a hematopoietic neoplasia that invades the lymphoid organs. It arises from the lymphoid tissues that include the spleen, lymph nodes, and the gut-associated lymphoid tissue within the digestive, respiratory, and urogenital tracts [1,2,4]. Confusion has arisen in the past about the classification of lymphoma versus leukemia. Leukemia arises from cells of the bone marrow, where there is a form known as lymphoid leukemia which arises in the cells of the bone marrow, but not specifically the lymphoid tissue [2]. Lymphoma can develop from two different cell lineages, B-cell or T-cell, or both cell lineages. The most common type in the equine species is T-cell lymphoma.

There are four forms of equine lymphoma: generalized or multicentric lymphoma, alimentary or intestinal lymphoma, mediastinal/thoracic or thymic lymphoma, and cutaneous lymphoma [1, 2, 3, 12]. The most common form of equine lymphoma is the generalized or multicentric form [1,12]. The most common tumor of the equine intestinal tract is alimentary or intestinal lymphoma [12]. Generalized or multicentric lymphoma typically invade multiple organs and by the time the disease is noticeable it has progressed throughout the body and causes systemic illness.

The exact mechanism of lymphoma transformation in the equine species has not been studied enough to describe definitively. The transformation in oncology refers to the change that a normal cell undergoes as it becomes malignant. Immunophenotyping of the tumors has been studied in the human population and lymphoid tumors are being classified, however there is not enough evidence to classify within the equine species [1].

Diagnostic Approach and Differential Diagnosis:

Equine lymphoma typically presents with nonspecific clinical signs that can lead one to consider many different disease processes. Upon presentation, one should develop a problem list followed by differential diagnoses so that one can develop a plan to systematically rule out via diagnostic tests. A few common differential diagnoses that can be seen in a patient presenting with vague, non-specific clinical signs include: heart failure, granulomatous inflammation, abscesses, and metastatic carcinomas.

A thorough physical exam should be performed on every animal. A basic physical exam can be unremarkable or show significant diagnostic findings. Typical findings may include subcutaneous edema, ocular or nasal discharge, and lymphadenopathy. In 50% of cases the physical exam is completely normal.

After a complete physical exam and palpation have been performed, a complete blood count and serum biochemistry should be completed to help differentiate and rule out other diseases. CBC findings are frequently non-specific and include anemia, lymphopenia or lymphocytosis, leukopenia, hyperfibrinogenemia, and thrombocytopenia [1,2]. A common hematological abnormality found includes anemia. Anemia can be noted in cases of equine infectious anemia, autoimmune hemolytic anemia, or plasma cell myelomatosis [4].

Hematological changes seen on a serum biochemistry may include hypoalbuminemia, hyperglobulinemia, and changes indicating diminished organ function [1, 2].

Ultrasonographic examination of the thorax and abdomen can be used to identify organ systems involved in the disease process. On ultrasound, the different organs can be evaluated for lesions and/or masses present. The gastrointestinal tract is often affected diffusely, which on ultrasound can be indicated by irregular, thickened, or enlarged sections of small intestines. The most common organs to find affected via ultrasound include the liver, spleen, heart, lymph

nodes, and kidney. The most typical lesion is the development of masses within the organs. Radiographic examination of the thorax is difficult to obtain and interpret in the equine species due to their enormous size, and have a markedly decreased sensitivity compared to other species. However, they can help reveal enlargements within the thoracic cavity such as the cardiac silhouette. They are also great to assess the lungs for possible metastatic lesions.

Aspiration and biopsy are the preferred methods of diagnosis, however can typically be very difficult to obtain based on the location of lesions being in the thorax and abdomen. Ultrasound guided fine needle aspiration and biopsy can also be performed when a mass is detected to determine the pathology within the specific organ. Cytology and histology of the samples should be submitted. Tissue samples via biopsy allow the disease to be categorized into the B or T cell origin. Tissue samples also can be used to stage the neoplasia, determine the proliferation rate, and determine if there are hormone receptors present at that time period. Common histological findings of equine lymphoma include compression or destruction of the normal tissue architecture, unorganized chromatin within the single populations of lymphoid cells, inconsistent size, shape, and number of cells. Bone marrow aspirate and core biopsy can be used to identify disseminated lymphoma. Cytology and histology of the bone marrow samples typically exhibit mixed small to medium sized nucleated lymphocytes that infiltrate the normal architecture of the bone marrow [9].

Unfortunately, the majority of equine lymphoma diagnoses are confirmed post-mortem at necropsy. During post mortem examination, multiple organs are typically infiltrated with disease that wasn't noted ante mortem. Histological samples display multiple areas of dense lymphoid infiltration, most commonly with small to medium sized lymphocytes [9]. Lymphoid tissue, including but not limited to lymph nodes, are enlarged and appear to have an abnormal color,

which is typically a yellow to brown color change [9]. The spleen, liver, kidneys, and large colon typically exhibit infiltration of abnormal lymphocytes in the sections obtained [9].

Treatment and Management:

Treatment of lymphoma in the equine species is a very limited topic [12]. Treatment of this disease should be extensively discussed with an owner prior to starting therapy. The effectiveness of therapy will depend highly on the stage of disease, effected organs, owner compliance, willingness, and financial status [1,2,4]. The amount of scientific data on the treatment is limited. There are several different treatment options that have been developed either through research or by mimicking the treatment protocols in human and other species of veterinary medicine [12]. Treatment options can be grouped into ablation (surgical), cytotoxic (radiotherapy, chemotherapy), and biological (immunotherapy) [12]. At times, all therapies may be combined to get the best results. Surgical excision involves removing the entire localized tumor, and has the best prognosis in well circumscribed, locally invasive tumors [12]. Surgical excision is not always completely curative, and is typically combined with other forms of therapy such as chemotherapy or radiotherapy [12].

Chemotherapy was once not a treatment option in the equine species because of the cost and potential toxicity [12]. Due to the development of generic forms and different administration routes, it is now an option [12]. Chemotherapeutic options are more limited than in small animals or humans. Most chemotherapy protocols in small animal and human medicine, involve combination therapy, however in the equine species systemic treatment typically includes only one chemotherapeutic agent [12]. Curative chemotherapy is only possible in solitary masses [2]. Most chemotherapy protocols are based on the drug dose which uses a

formulation based on surface area [2]. There have been studies to find that after the start of chemotherapy there is remission of disease within 2-4 weeks [2]. Even though remission is noted, therapy should be continued for an additional 2-3 months [2]. Typical chemotherapeutic medications can include cyclophosphamide, chlorambucil, cytosine arabinoside, doxorubicin, vincristine, prednisolone, L-asparaginase, or cisplatin [2]. While multi-drug protocols may include several different combinations of the individual drugs [2].

Radiotherapy uses x-rays to kill abnormal cancer cells [12]. In the equine species, it is most beneficial to treat localized tumors that have bony involvement [12]. The use of radiotherapy is limited, due to the limited facilities that perform this treatment. There are 2 techniques used in radiotherapy: brachytherapy or teletherapy [2]. Brachytherapy uses a sealed radioactive source such as iridium-92, iodine-125, or strontium-90 [2]. The source is either implanted or used on the surface of the target tissue [2]. Teletherapy is used to treat smaller, more superficial tumors [2]. Radiation therapy is done in as few treatments as possible, and can have several side effects [2]. Side effects can include ulceration, inflammation, and necrosis of treated tissues [2].

Prognosis:

The prognosis of most forms of equine lymphoma is poor. By the time that the horse is diagnosed with this neoplasia, the horse is typically too debilitated to recover and go through therapy. Anecdotal therapy is typically used if an owner elects any type of therapy, it is the treatment of disease based on clinical experience and not scientific proof of success. The major limiting factor in any therapy, is the lack of diagnosis early in the disease process [11]. Horses typically do not recover from lymphoma, even after therapy. Equine lymphoma is a progressive

malignant disease. Although, there is no cure or completely successful therapy known, the treatment options available have shown the ability to slow the disease process and prolong the life of the animal. There have been reports of the cutaneous form being responsive to steroid therapy, and persists over years. Ultimately, equine lymphoma carries a very poor prognosis and most horses are humanely euthanized due to the extent of disease.

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