LYMPHOMA IN HORSES: WHAT WE KNOW AND DON’T KNOW

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INTRODUCTION
Lymphoma in horses is relatively rare when compared with the frequency with which it is diagnosed in humans and small animals; however, of the non-dermatological neoplasms of horses, it is the most common. Lymphoma is a malignant, hematopoietic neoplasm that arises from lymphatic tissue. When it originates in the bone marrow it is designated leukemia versus when it originates in the periphery (lymph nodes, spleen, liver, etc.) it is designated lymphoma. The additional nomenclature can be confusing and is best described by applying the World Health Organization classification scheme which aims to “integrate knowledge of topography, cell morphology, immunophenotype, genetic features, and clinical presentation and course”.[1] By this method, researchers have identified that T-cell rich large B-cell lymphoma is the most common in the horse, however 14 subtypes were identified in the study. Additional nomenclature used in horses includes classifying the neoplasia relative to the topography: multicentric or generalized, alimentary, mediastinal, cutaneous, and solitary tumors of extranodal sites.[2] Historically, lymphoma has no breed or sex predisposition and any age animal can be affected.[2] Lymphoma has been reported in newborn foals and older horses, though most horses are between 4-10 years of age.

CLINICAL SIGNS
Clinical signs of lymphoma are variable based on origin of the tumor, degree of metastasis, location of the tumor(s), etc. When the tumors interfere with normal physiological and anatomical functions, clinical signs arise bringing awareness to owners and handlers. In the author’s experience, horses are quite good are carrying-on through the early stages of the disease progression making prompt diagnosis, and subsequent successful treatment, a challenge. One exception are horses with the cutaneous form of lymphoma. While early diagnosis is still difficult, the nature of the outward dermatological lesions means that cutaneous lymphoma may be more promptly recognized by the owner or handler. General, non-specific, clinical signs may include lethargy, weight loss, changes in appetite, changes in attitude, and decreased performance; and specific signs are related to tumor interference with anatomy and physiological processes, as mentioned above.

DIAGNOSIS
Confirmation of internal (non-dermatological) neoplasia in horses can be diagnostically challenging due the large body size of most horses, limited imaging techniques (particularly in the field setting), financial expense for evaluation, and low sensitivity/specificty for many diagnostic modalities. However, with a logical combination of diagnostic techniques, a diagnosis of lymphoma can routinely be made. Multiple modalities are available to help determine if neoplasia is a cause for the horse’s chief complaint/clinical signs with some tests/procedures being more valuable based on the body system affected. Ultimately, a problem-oriented approach based on identification of clinical problems from the history and physical examination helps to prioritize the diagnostic efforts. The author takes the approach of identifying or hypothesizing which body system(s) is affected, how the anatomy may be impacted, and what pathophysiology could lead to the clinical signs. This typically results in a logical starting point for prioritizing the diagnostic evaluation.

When presented with a horse showing non-specific clinical signs (i.e., signs cannot easily be attributed to one body system to guide diagnostic efforts), it is reasonable to perform diagnostic tests aimed at providing a starting point for more aggressive investigation. Typically, this may include gathering data from standard blood work (CBC, serum biochemistry, urinalysis); recognizing that cytology of the blood and urine is needed. Additionally, thoracoabdominal ultrasonography may provide immediate diagnostic feedback to guide additional diagnostic tests. For example, if you perform an abdominal ultrasound examination and recognize free peritoneal fluid, an abdominocentesis might be the next logical step along with transrectal abdominal palpation. Sampling of identified masses and/or the fluid surrounding the masses can be valuable as lymphoma tumors may exfoliate cells into the fluid, and, of course, direct sampling by fine needle aspirate or needle biopsy provides a definitive diagnosis. The author uses abdominocentesis in almost all horses in which non-specific clinical signs are expressed. While a normal analysis of abdominal fluid does not exclude lymphoma as a diagnosis, frequently the abdominal fluid shows neoplastic cells, providing an indirect diagnosis. Similarly, transrectal abdominal palpation should be standard component of the physical examination when non-specific signs, signs related to the gastrointestinal tract, or signs of neoplasia are noted. For conditions of the thoracic cavity, thoracocentesis can be utilized, but only when free pleural fluid is evident on ultrasonography; however,
transtracheal wash or bronchoalveolar lavage may be useful in showing cytological evidence of lymphoma in the pulmonary parenchyma.

Fine needle aspirate (FNA) and biopsy of the regional lymph nodes and masses are routinely performed in small animal medicine, and they can be easily performed in horses as well. The mandibular lymph nodes are the only palpable regional lymph nodes in a horse and for the purposes of characterizing disease, FNA of the mandibular lymph nodes should be routine. The samples are submitted for cytological analysis and may direct further investigation. When the lymph nodes are enlarged, or other masses are apparent in the skin (e.g., cutaneous lymphoma) excisional biopsy can be performed for histological evaluation. When masses are identified in the abdomen, ultrasound-guided FNA or needle biopsy can be performed. In the author’s experience, this is a critical piece for ante-mortem diagnosis of neoplasia in the abdominal cavity. While the anatomy at times may obstruct sample collection (e.g., an organ or vessel is positioned between the body wall and the mass), FNA is usually feasible and safe, and facilitates direct evidence of a neoplastic condition.

Additional diagnostic efforts can be directed to other body systems or be escalated to more aggressive approaches when needed. For example, bone marrow aspirate and core biopsy can be performed when leukemia is suspected or when lymphoma has spread to the bone marrow. Typically bone marrow examination is a routine part of staging of the disease process which is needed when developing a therapeutic plan or prognosis. Or in the event of persistent gastrointestinal clinical signs in the absence of a diagnosis, exploratory laparotomy may be performed. For cases of cutaneous lymphoma, excisional biopsy of visible skin lesions for histopathology is the logical and best diagnostic step. Subsequent staging of the disease process is necessary to determine prognosis and therapeutic options.

Once a horse has been definitively diagnosed, if biopsy tissue is available, immunotyping is valuable to help determine the cell type affected and to subsequently guide therapy.

**STAGING**

Staging of neoplastic conditions is necessary when considering a therapeutic plan and when providing a prognosis. In the author’s experience, many horses are presented for evaluation once the lymphoma has metastasized or invaded the tissue of origin to such an extent that therapy is unrewarding; however, when diagnosed early, or in cases of cutaneous lymphoma, therapy can be successful or extend-life. Staging involves determining the extent of disease progression and presence of metastases. In horses, staging includes diagnosis of the primary site of neoplasia; spread to regional lymph nodes or other organs; and recognition of systemic or regional clinical signs. For the author, staging of a horse that has been definitively diagnosed with lymphoma involves the following diagnostic modalities: physical examination, CBC/chemistry/urinalysis, thoracoabdominal ultrasonography, FNA of the mandibular lymph nodes, thoracic radiography, and bone marrow aspirate.

**ON THE HORIZON**

What veterinarians know about lymphoma in horses is growing every day, but remains relatively limited when compared to human medicine and small animal medicine. To some degree, this is due to the decreased incidence of lymphoma in horses as compared to humans and small animals, but this is also impacted by the progression of the disease in horses. As mentioned previously, horses are good at not showing clinical signs early in the progression of the disease; therefore prompt diagnosis and subsequent successful treatment is a challenge. Veterinarians are usually making the diagnosis at the end-stage of the progression of disease when therapeutic intervention is unlikely to help and the horses are euthanized. However, clinicians are frequently evaluating different treatment options to determine which options have the best outcome. Chemotherapy, surgical excision, and radiation therapy are options and may provide significant palliative or curative treatment.[3, 4]

Similarly, there are questions that remain regarding possible inciting causes for lymphoma in horses. Recently, equine herpesvirus 5 has been identified in horses with lymphoma.[5] The question remains, however, if this is a causative agent. As more information becomes available, classification of lymphomas in horses may change.

**SUMMARY**

Lymphoma, while not as commonly diagnosed by equine veterinarians as compared to veterinarians who work with small animals, remains a common neoplastic disease of horses and should be a differential diagnosis.
when evaluating horses of any age for non-specific clinical signs that persist or worsen. Diagnostic efforts should be aimed at identifying the primary site of the tumor and subsequently determining if the disease has metastasized to other organs/body systems. Based on the stage, horse compliance, owner finances, and the owner acknowledging the advantages and limitations of therapy, a therapeutic plan can be developed to hopefully prolong life or make the horse comfortable.

REFERENCES