Use of chemotherapy for treatment of a mixed-cell thoracic lymphoma in a horse

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A 4-year-old Oldenburg mare (weight, 610 kg [1,340 lb]) was evaluated because of a 4-day history of anorexia, coughing, and pyrexia of unknown origin. Prior to admission, the referring veterinarian had administered phenylbutazone (2 g, PO, q 12 h) and cefitiofur sodium (1 g, IM, q 12 h). The owner reported that the horse coughed during exercise and displayed minimal interest in its immediate surroundings.

On physical examination (day 1), the mare was obtunded, pyrexic (rectal temperature, 40°C [104°F]), and coughed occasionally. On thoracic auscultation, wheezes were detected bilaterally in the dorsocaudal lung fields; serous, nonodorous nasal discharge was evident bilaterally. Thoracic ultrasonography revealed a small amount of pleural fluid in both lungs; radiography revealed a focal, poorly defined, 8-cm-diameter opacity between the carina and diaphragm. To evaluate the respiratory tract further, a tracheal aspirate specimen was obtained with 40 mL of lactated Ringer's solution withDivision of Infectious Diseases and Pathology, College of Veterinary Medicine, Oregon State University, Corvallis, OR 97331 (Saulez, Schlipf, Cebra, Bird); and the Department of Biomedical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853-6401 (McDonough). Dr. Saulez’ present address is Hagyard-Davidson-McGee Associates PSC, Medical Facility, 4250 Iron Works Pike, Lexington, KY 40511-8412.

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discontinued on day 5 as a result of progressive improvement in appetite and oral intake of fluids. Treatment with pentoxifylline and nitroglycerin was discontinued on day 7 because digital pulses were within reference limits. On day 8, results of hematologic analyses indicated less severe leukocytosis (14,400 WBCs/µL), mature neutrophilia (11,376 cells/µL), and hyperfibrinogenemia (500 mg/dL). Administration of gentamicin was discontinued on day 8; treatment with penicillin G potassium and metronidazole was discontinued on day 9. Because of incomplete resolution of the chronic active inflammation, administration of a potentiated sulfonamide (25 mg/kg, PO, q 12 h) was begun on day 9. The horse was discharged on day 11.

Three days after discharge from the hospital (day 15 with regard to the initial examination), the horse was readmitted for further evaluation after an acute episode of colic that morning; the referring veterinarian had administered flunixin meglumine (1.1 mg/kg, IV). On examination, the mare was tachycardic (60 beats/min) and tachypneic (44 breaths/min), with bilateral wheezes audible via auscultation of the thorax. Findings of rectal palpation and cytologic examination of peritoneal fluid obtained via abdominocentesis were within reference limits. Edema in the pectoral region and pitting edema of both forelimbs were evident. Abnormalities identified via hematologic and serum biochemical analyses included leukocytosis (14,600 WBCs/µL) as a result of mature neutrophilia (10,366 cells/µL) and band neutrophilia (876 bands/µL), normochromic, normocytic anemia (PCV, 26%; reference range, 32% to 48%), hyperfibrinogenemia (500 mg/dL), hypalbuminemia (2.6 g/dL), and hyperglobulinemia (3.9 g/dL). A 10-cm-diameter, well-defined opacity was detected radiographically between the carina and diaphragm (in the region in which the poorly defined opacity was previously detected radiographically). Thoracic ultrasonography revealed a large amount of pleural fluid, particularly in the right hemithorax. Because of the findings of radiographic and ultrasonographic evaluation of the thorax and abdomen, pleurodynia was thought to be the most likely cause of the episode of colic.

Drainage of the left and right hemithoraces yielded 1 and 7 L of cloudy pleural fluid, respectively. The pH of the pleural fluid from the left hemithorax was 7.3 (reference limit, 7.3 ± 0.1), the glucose concentration was 138 mg/dL (reference limit, 97.2 ± 33.5 mg/dL), and the lactate concentration was 2.23 mmol/L (reference limit, 1.63 ± 1.2 mg/dL).1 Biochemical analysis was not performed on the pleural fluid from the right hemithorax.

The fluids obtained from both pleural spaces were cytologically similar (Table 1). The pleural fluid from the left and right hemithoraces was red and yellow, respectively, and contained 35,000 and 27,000 nucleated cells/µL (reference range, < 10,000 cells/µL), respectively; the total protein concentrations in both samples were characteristic of an exudate (4.2 g of protein/dL of pleural fluid). Lymphocytes predominated in both samples of pleural fluid (composing 50% of cells in the fluid in the left hemithorax and 65% of cells in the fluid in the right hemithorax); large numbers of prolymphocytes and lymphoblasts were observed, although small lymphocytes predominated (Fig 1). In some of the large lymphocytes, nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebbing, cleaved nuclei, and occasional clover-shaped nuclear blebling.
leaf-shaped nuclei were detected. Scattered mitotic figures (0 to 2/hpf) were observed, but few of these were considered abnormal cytologically (Fig 2). Additionally, numerous large mononuclear cells were present in both samples (comprising 23% of cells in the fluid in the left hemithorax and 22% of cells in the fluid in the right hemithorax), and leukophagocytosis was common among the mononuclear cells in both fluid samples. The findings of the cytologic evaluation of pleural fluid samples obtained on day 15 were consistent with lymphoma with secondary chronic inflammation.

To further classify the lymphoma, samples of pleural fluid were cytocentrifuged to obtain cells for immunophenotyping. Immunophenotyping (based on a previously described technique2) was performed on 5 x 10⁴ cells with streptavidin-horseradish peroxidase.3 Briefly, cells were centrifuged onto glass slides, fixed in acetone for 2 minutes, and air-dried. The slides were rinsed with phosphate-buffered saline (PBS) solution. Endogenous peroxidase was blocked with 0.3% hydrogen peroxide in 0.1% sodium azide in PBS solution for 15 minutes and then blocked with 10% horse serum for 10 minutes at room temperature (20ºC). Primary antibodies (BLA36+ [mouse monoclonal], CD79α [mouse monoclonal], and CD3 [rabbit polyclonal])4 were diluted for optimum reactivity as established by titration and applied for 2 hours at 37ºC. Slides were rinsed in PBS solution and incubated with prediluted biotinylated horse anti-mouse IgGm for 20 minutes at room temperature (20ºC). After rinsing with PBS solution, slides were incubated with the streptavidin-horseradish peroxidase conjugate for 15 minutes at room temperature (20ºC). Slides were again rinsed with PBS solution, and the chromagen was applied. Color development was monitored by examination under the light microscope, and the reaction was stopped by placing the slides in distilled water. Counterstaining with Gill's No. 2 hematoxylin was performed for 2 minutes, followed by a rinse in tap water; slides were placed into PBS solution and then placed into distilled water. Finally, the slide preparations were coverslipped by use of a mounting medium5 and examined via light microscopy. Negative controls were also prepared; slides were processed in the same manner except that the primary antibody was substituted with normal mouse ascites,6 normal rabbit serum,7 or rabbit isotype control immunoglobulin. In the negative control slides, no cells were stained when the primary antibody was substituted with normal mouse ascites, normal rabbit serum, or rabbit isotype control immunoglobulin.

On examination of the slides, > 95% of the small lymphocytes (Fig 3) were CD3+ T cells, whereas most of the large lymphocytes (Fig 4) were BLA36+ B cells. A small proportion (5% of the 2 cell types combined) of large lymphocytes and plasma cells were CD79+. Large lymphocytes had weak cytoplasmic staining when labeled with a pan-equine immunoglobulin reagent, and results for IgG, IgM, and IgA were nega-

Figure 2—Photomicrograph of a preparation of pleural fluid from a 4-year-old horse with thoracic lymphoma. Notice that the lymphocytes often contain indented or cleaved nuclei and occasional cells have ring-shaped nuclei; approximately 10% of lymphocytes contain small azurophilic granules. Mitotic figures are observed scattered throughout the sample. Wright-Giemsa stain; bar = 10 μm.

Figure 3—Photomicrograph of a preparation of pleural fluid from a 4-year-old horse with thoracic lymphoma. Notice that the cytoplasmic membranes of > 95% of the small lymphocytes have reacted positively with anti-CD3+ antibody by use of the streptavidin-biotin-peroxidase method with Gill’s hematoxylin counterstain. Bar = 10 μm.

Figure 4—Photomicrograph of a preparation of pleural fluid from a 4-year-old horse with thoracic lymphoma. Notice that almost all large lymphocytes have reacted positively with anti-BLA36+ antibody by use of the streptavidin-biotin-peroxidase method with Gill’s hematoxylin counterstain. Bar = 10 μm.
concentrative. The large lymphocytes were strongly positive for both k and la light chains. Results of immunophenotyping indicated a mixed-cell (T-cell-rich, B-cell) lymphoma.

The horse continued to receive a potentiated sulphanamide (25 mg/kg, PO, q 12 h) and flunixin meglumine (1.1 mg/kg, IV, q 12 h) because of ongoing chronic active pulmonary inflammation. On day 17, the mare had an acute episode of tachycardia (66 beats/min) and tachypnea (72 breaths/min); wheezes and crackles associated with respiration were auscultated bilaterally. Results of hematologic analyses indicated mature neutrophilia (5,700 cells/µL), band neutrophilia (1,000 cells/µL), hyperfibrinogenemia (600 mg/dL), and continued normocytic, normochromic anemia (PCV, 24%). Thoracic ultrasonography of the left hemithorax revealed poor pulmonary excursion, fibrin, and small amounts of cloudy pleural fluid, compared with the right hemithorax. Via thoracocentesis of the left hemithorax, a specimen of yellow, cloudy pleural fluid was obtained; 0.5 L of fluid was drained. The protein concentration of the pleural fluid was 5.7 g/dL. Findings of cytologic examination of the Pleural fluid were consistent with marked suppurative exudate. Although bacteria were not observed (and after bacteriologic culture of the fluid, there was no growth of microorganisms), sepsis was likely because the Pleural fluid was slightly acidic (pH, 6.9) with low glucose concentration (<10 mg/dL) and high lactate concentration (11.61 mmol/L). Therefore, to control the cose concentration (of microorganisms), sepsis was likely because the thoracic ultrasonography of the left hemithorax revealed poor pulmonary excursion, fibrin, and small amounts of cloudy pleural fluid, compared with the right hemithorax. Via thoracocentesis of the left hemithorax, a specimen of yellow, cloudy pleural fluid was obtained; 0.5 L of fluid was drained. The protein concentration of the pleural fluid was 5.7 g/dL. Findings of cytologic examination of the Pleural fluid were consistent with marked suppurative exudate. Although bacteria were not observed (and after bacteriologic culture of the fluid, there was no growth of microorganisms), sepsis was likely because the thoracic ultrasonography of the left hemithorax revealed poor pulmonary excursion, fibrin, and small amounts of cloudy pleural fluid, compared with the right hemithorax. Via thoracocentesis of the left hemithorax, a specimen of yellow, cloudy pleural fluid was obtained; 0.5 L of fluid was drained. The protein concentration of the pleural fluid was 5.7 g/dL. Findings of cytologic examination of the Pleural fluid were consistent with marked suppurative exudate. Although bacteria were not observed (and after bacteriologic culture of the fluid, there was no growth of microorganisms), sepsis was likely because the pleural fluid was slightly acidic (pH, 6.9) with low glucose concentration (<10 mg/dL) and high lactate concentration (11.61 mmol/L). Therefore, to control the pleuritis, the antimicrobial treatment was changed to penicillin G potassium (22,000 U/kg, IV, q 6 h) and gentamicin (6.6 mg/kg, IV, q 24 h), and flunixin meglumine (1.1 mg/kg, IV, q 12 h) was administered. Within 24 hours, the horse's clinical status had improved and no further abnormal lung sounds could be auscultated.

On day 18, results of hematologic analyses indicated band neutrophilia (170 cells/µL) and normocytic, normochromic anemia (PCV, 22%). Repeated thoracic evaluation via ultrasonography revealed a solitary, homogenous 4.5-cm-diameter mass on the cranial mediastinum surrounded by anechoic pleural fluid. Transabdominal ultrasonography was performed (with particular attention to examination of the spleen and liver), and findings were within reference limits. Serum protein electrophoresis revealed a high β2-globulin concentration (1.1 g/dL, reference range, 0.31 to 0.93 g/dL) that was consistent with chronic inflammation. Treatment with penicillin G potassium and gentamicin was discontinued on day 22 as a result of improvement in clinical signs and ultrasonographic abnormalities.

The horse remained bright with a good appetite and maintained its body weight. Following consultation with the clients, chemotherapy was started; cytarabine (170 mg/m2, IM) was administered on days 31 and 45, alternating with cyclophosphamide (142 mg/m2, IV) administered on days 38 and 52. No adverse reaction was noted during administration of the chemotherapeutic agents. Treatment with prednisolone (86 mg/m2, PO, q 48 h) was initiated on day 31, and the horse was closely monitored for signs of laminitis. On day 33, a mild amount of pleural fluid was visualized on ultrasonographic images of the left hemithorax and thoracentesis was performed; 0.01 L of yellow fluid (protein concentration, 3.5 g/dL) was drained. The sample of pleural fluid was classified as a suppurative exudate via cytologic evaluation, and no neoplastic cells were observed. Several abnormalities were identified via serial hematologic analyses: on day 31, normocytic, normochromic anemia resulting from chronic disease (PCV, 30%) and hyperfibrinogenemia consistent with chronic inflammation (700 mg/dL) were detected, both of which resolved by day 36; and on day 63, thrombocytopenia (35 X 109 platelets/µL; reference range, 100 to 600 X 109 platelets/µL) was detected, which resolved by day 68.

On day 64, repeated thoracic ultrasonography revealed no abnormalities and radiography revealed marked regression of the thoracic opacity caudal to the heart (to <2 cm in diameter, with poorly defined margins). The mare was discharged on day 68, and the owners were instructed to allow a 3-month period of rest before resuming controlled exercise and to administer prednisolone (86 mg/m2, PO, q 48 h) to the horse for the remainder of its life. At 3 and 6 months after discharge, radiographic evaluations of the thorax revealed no discernible opacity between the cardia and diaphragm; no mediastinal mass was detected via thoracic ultrasonography. All variables assessed via hematologic and serum biochemical analyses were within reference limits. Eight months after discharge, the horse was reported to be in good health and had resumed light exercise.

There are numerous reports of thoracic tumors in horses, including pulmonary carcinoma, chondrosarcoma, bronchial myxoma, granulosa cell tumor, pleural mesothelioma, thymoma, and lymphoma. Lymphoma is the most common form of thoracic tumor in horses and has traditionally been classified on the basis of anatomic distribution, namely mediastinal, alimentary, multicentric, cutaneous, and generalized forms. However, more precise and relevant classifications require integration of immunophenotypic, molecular, and clinical data to identify distinct entities. Reports have focused on clinical signs and clinicopathologic findings. Malignant lymphoma that is confined to 1 organ (eg, the thorax) is rare in humans and, to the authors' knowledge, has not been previously reported in equids.

Primary thoracic lymphoma appears to be rare in horses and produces minimal clinical signs in early stages; it is commonly diagnosed when clinical signs are pronounced or when metastasis has occurred to other organ systems.

The horse of this report was initially evaluated because of signs of lower airway disease. Neoplastic cells were not identified in the fluid sample obtained via the initial thoracocentesis (as previously reported in a 7-year-old mare with primary pulmonary carcinoma) or in the tracheal aspirate specimen (as previously reported in specimens obtained from 13 horses with lymphosarcoma and 1 each with pulmonary carcinoma, mesothelioma, squamous cell carcinoma, and renal carcinoma). Therefore, the absence of neoplastic cells in pleural fluid or tracheal aspirate specimens...
is not conclusive evidence for the absence of a thoracic tumor. The apparent lack of neoplastic cells in these samples may be the result of intermittent shedding of tumor cells (perhaps because populations of neoplastic cells have become sequestered) or an inability to retrieve fluid from the caudal lung lobes via transendoscopic lavage. In the horse of this report, other diagnostic modalities that could have been used included percutaneous transthoracic fine-needle aspiration or biopsy of the mediastinal or pulmonary mass.18

Recent advances in molecular biology involving immunohistochemical evaluation of formalin-fixed tissue have been applied to the investigation of lymphomas in horses; in 1 study,11 of 24 (46%) horses had tumors that were classified as T-cell-rich, B-cell lymphomas. To the authors’ knowledge, immunophenotyping has not been described as an aid to classification of thoracic lymphomas in horses. This technique should be considered when atypical lymphoblasts are detected in pleural fluid, thereby enabling classification of the type of lymphoma without requiring invasive techniques to obtain tissue samples. At present, immunophenotyping is a standard technique in human medicine, but the diagnosis of lymphoma subtypes depends on histologic assessments, and not all tumor subtypes are solely defined by cytochemical criteria.19

Detection of a mixture of small and large lymphocytes histologically or cytologically is indicative of 1 of 2 types of B-cell lymphoma. A diffuse mixed-cell type (also known as a centroblastic-centrocytic lymphoma according to the Kiel classification) can develop and consists entirely of B cells.20 Also, a T-cell-rich, B-cell lymphoma can develop with a mixture of large and small lymphocytes; this is composed mostly of small tumor infiltrating (reactive) T cells and lesser numbers of neoplastic B cells.20 These B cells, as observed in the horse of this report, are cytologically atypical and have large vesicular nuclei with prominent nucleoli and peripheral distribution of chromatin.

Few reports21 22 have described the use of a multiple-drug induction protocol in the chemotherapy treatment of lymphoma in horses. One such protocol consisted of cytarabine (200 to 300 mg/m², SC or IM, q 7 to 14 d), chlorambucil8 (20 mg/m², PO, q 14 d) or cyclophosphamide (200 mg/m², IV, q 14 to 21 d), and prednisone (1.1 to 2.2 mg/kg [0.5 to 1 mg/lb], PO, q 48 h). Administration of vincristine (0.5 mg/m², IV, q 7 d) can be added to the induction protocol if no clinical response is detected in the first 2 to 4 weeks of treatment with the chemotherapeutic agents.19 Should remission be achieved, the induction protocol can be used for an initial 2- to 3-month period; this is followed by a maintenance protocol during which the dose of prednisolone is gradually reduced and the administration interval for each chemotherapeutic drug is extended by 1 week for the next 2 to 3 months. Finally, the administration interval for each chemotherapeutic drug is extended by another week for the next 2 to 3 months until termination of chemotherapy in 6 to 8 months.21 Other reported protocols include cyclophosphamide (200 mg/m², IV, q 14 to 21 d) or l-asparaginase3 (10,000 to 40,000 U/m², IM, q 14 to 21 d) and combinations of cytarabine or cyclophosphamide with prednisone.1 In humans, treatment of T-cell-rich, B-cell lymphomas is similar to that used for diffuse B-cell lymphoma and involves the administration of cyclophosphamide (750 mg/m², IV), doxorubicin9 (50 mg/m², IV), vincristine (1.4 mg/m², IV), rituximab10 (375 mg/m², IV), and prednisolone (50 mg/m², PO, q 24 h for 5 days).22

The most commonly encountered complications associated with administration of chemotherapeutic drugs in equids include anorexia, signs of depression, jugular thrombosis, laminitis, bone marrow damage, gastrointestinal and genitourinary tract toxicoses, and immunosuppression.23 Anemia and thrombocytopenia may develop as a result of bone marrow suppression, as detected in the horse of this report; depending on the severity of anemia and thrombocytopenia, blood transfusions may be warranted or further chemotherapeutic treatments postponed. Leukopenia and secondary infection are more commonly encountered; however, recommendations vary regarding the lower limit of WBC concentration at which chemotherapy should be suspended.24

Pharmacodynamics may influence selection of chemotherapeutic agents. Cytarabine administered IV is rapidly metabolized, compared with its metabolism after IM administration,25 whereas cyclophosphamide requires bioactivation to its active metabolite 4-hydroxyxyclophosphamide by the liver microsomal oxidase system.26 In the treatment of horses with lymphoma, considerable success has been achieved with a chemotherapeutic protocol consisting of cytarabine, cyclophosphamide, and prednisolone.27 Cytarabine is cytotoxic to proliferating cells, and its action is specific for cells undergoing DNA synthesis.28 After hepatic bioactivation, cyclophosphamide interferes with the growth of proliferating malignant cells by causing cross-linking of tumor cell DNA.29 Corticosteroids are thought to initiate cell death by activation of endonucleases that destroy chromatin integrity in tumor cells.30

Primary lymphoma in horses is rare but may be treatable when diagnosed early. Immunophenotyping has been used to identify monoclonality in effusions as an indication of lymphomatous involvement in human medicine31; however, clinicians should be aware that large numbers of reactive T cells may obscure detection of a population of neoplastic B cells.32 Immunophenotyping in conjunction with fine-needle aspiration and biopsy may be useful in the diagnosis, subtyping, and treatment of lymphoma.15

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