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ACUTE LYMPHOBLASTIC LEUKEMIA IN A JUVENILE SOUTHERN BLACK RHINOCEROS (*DICEROS BICORNIS MINOR*)

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Abstract: A 2-mo-old female southern black rhinoceros (*Diceros bicornis minor*) developed acute upper respiratory dyspnea, in association with lymphadenopathy and marked immature lymphocytosis. A diagnosis of acute lymphoblastic leukemia was reached on the basis of the morphologic and cytochemical characteristics of peripheral lymphoblasts. Antineoplastic chemotherapy included administration of cytarabine, cyclophosphamide, vincristine, and doxorubicin, with clinical remission achieved 19 days after initiation of treatment. The rhinoceros died, however, of congestive heart failure, presumably secondary to doxorubicin cardiotoxicity and a particular sensitivity of rhinoceros myocardial tissue to free hydroxyl radicals. The pharmacologic effects of any therapeutic agent need to be carefully considered before use in the black rhinoceros, especially within the context of the unique physiology of this species.

Key words: Black rhinoceros, *Diceros bicornis*, leukemia, chemotherapy, lymphoblast, granulocyte colony stimulating factor.

INTRODUCTION

Leukemias are uncommon in animals and often remain untreated in large domestic species.[1] This report details the medical management of acute lymphoblastic leukemia (ALL) in a juvenile southern black rhinoceros (*Diceros bicornis minor*), with emphasis on serial hematologic monitoring and the clinical and clinicopathologic responses to chemotherapy. Diagnosis and therapy of leukemia in this captive-born rhinoceros represented the combined efforts of both veterinary and human specialists and may provide guidelines for future management of neoplastic diseases in this highly endangered mammal.

CASE REPORT

A 21-mo-old female southern black rhinoceros calf ("Echo," estimated body weight 500 kg) developed acute signs of upper respiratory congestion on 21 September 1997 that were most noticeable during eating. Nasal swabs for bacterial and fungal cultures revealed only normal flora. Although a routine hemogram 6 wk earlier had been entirely normal, the white blood cell count (WBC) on day 2 was 49,093 WBC/μl (ref. range 6,900–15,400 WBC/μl).[2] Peripheral blood films were dominated (>90%) by a heterogeneous population of large (>25 μm) immature lymphoblastlike cells, including a full spectrum of forms between undifferentiated blasts and mature lymphocytes. The abnormal cells were morphologically most consistent with the L2 subtype of human lymphoblastic leukemia.[3] Mineral analytes revealed significant iron overload as demonstrated by up to threefold elevations in serum iron (245 μg/dl) and transferrin saturation (87%) and almost tenfold elevations in serum ferritin (995 ng/ml) when compared with six free-ranging *D. bicornis minor* sampled in Zimbabwe (Fe = 82–120 μg/dl, transferrin sat. = 22–34%, ferritin = 71–195 ng/ml).

A diagnosis of ALL was supported by negative cytochemical reactions for myeloperoxidase and nonspecific esterases and strong positive reactions for nuclear terminal deoxynucleotidyl transferase.[4] Flow cytometry confirmed the dominance of variably sized agranulocytic cells in a morphologic continuum with mature lymphocytes, distinctly separated from the monocyte–granulocyte series. Attempts to subclassify the leukemic population by reaction with a panel of monoclonal antibodies to human cell surface markers were unsuccessful. Evaluation of mononuclear cell cultures for reverse transcriptase and for viral particles via electron microscopy was negative, and therefore no evidence of retroviral-induced disease was found.

Nine days after the initial clinical signs, WBC peaked at 63,600/μl. On day 10, cytarabine (Cytosar U, Upjohn Co., Kalamazoo, Michigan 49001, USA; 1,000 mg i.v.) was given via the radial vein and oral prednisone therapy (Delatasone, Pharmacia & Upjohn Co., Kalamazoo, Michigan 49001, USA; 500 mg p.o.) was initiated. Within 12 hr, the calf's condition deteriorated, and the animal could

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Figure 1. A juvenile black rhinoceros (*Diceros bicornis minor*) with acute lymphoblastic leukemia. Enlargement of retropharyngeal lymph nodes (arrows) resulted in dyspnea.

walk only a short distance before returning to recumbency, exhausted. Administration of additional anti-inflammatory drugs, including flunixin meglumine (Banamine, Schering Plough Animal Health Corp., Kenilworth, New Jersey 07033, USA; 500 mg i.v.) and prednisolone sodium succinate (Solu-delta Cortef, Upjohn Co., 500 mg i.v.), resulted in transient respiratory improvement. Because of progressive dyspnea secondary to lymphadenopathy, cyclophosphamide (Neosar, Pharmacia Inc., Kalamazoo, Michigan 49001, USA; 1,000 mg i.v.) and ampicillin sodium (Amp-Equine, SmithKline Beecham Animal Health, West Chester, Pennsylvania 19380, USA; 9,000 mg i.v.) were administered on day 11, and the prednisone dosage was doubled to 500 mg p.o. b.i.d. Within 12 hr, respiration improved markedly, and although the WBC remained essentially unchanged at 50,350/μl, the relative percentage of circulating lymphoblasts decreased from 92% to 45%. On day 12, itraconazole therapy (Janssen Pharmaceutica, Beerse, Belgium, custom formulation by Mortar & Pestle Pharmacy, Des Moines, Iowa 50310, USA; 1,500 mg p.o.) was begun to preclude immunosuppression-related mycotic disease. By day 15, WBC had decreased to 38,900/μl, and the differential revealed a more mature population of lymphocytes, with blasts declining further to 28%. As estimated from peripheral blood smears, there were 16,500 platelets/μl (ref. range 158,000–467,000 platelets/μl).[1] By day 17, peripheral lymph node size had decreased by half, and the calf was less dyspneic. On day 18, cytarabine therapy (1,000 mg i.v.) was repeated, and vincristine sulfate (Oncovin, Eli Lilly & Co., Indianapolis, Indiana 46285, USA; 3 mg i.v.) was given the following morning because of a deterioration in the calf's condition. Within 24 hr of vincristine therapy, the WBC decreased to 28,450/μl, and the percentage of lymphoblasts in peripheral blood decreased to 3%. The calf's breathing had improved despite no visible change in lymphadenopathy (Fig. 1), and the calf developed several small (3–15 mm) cutaneous nodules on the left side of the neck and shoulder.

On day 22, the calf had an episode of epistaxis and resultant acute anemia (PCV = 17%; ref. range 37.5–51%). The calf was recumbent, with open-mouth breathing, marked lymphadenopathy, and mandibular edema. By day 23, the calf was unable to eat or drink because of severe dyspnea, and the WBC had risen to 60,725/μl because of an increased number of lymphoblasts. Because of this relapse, the calf was given diphenhydramine (Steris Laboratories Inc., Phoenix, Arizona 85043, USA; 500 mg i.v.) followed by a slow infusion of doxorubicin (Adriamycin RDF, Pharmacia Inc.; 200 mg i.v.; day 25). By the morning of day 27, the rhinoceros had markedly improved, with obvious reduction in the lymphadenopathy and mandibular edema. The calf regained its previous appetite and activity. There was corresponding hematologic improvement with decreases in WBC to 5,775/μl by morning and 3,375/μl by evening of day 27, with 72,000 platelets/μl. On day 29, the calf's breathing was normal, but the skin lesions enlarged and became fluid filled, and epistaxis returned. The PCV declined from 13% to 9% over the next 24 hr, and the calf received a blood transfusion. The donor was an adult male, wild-caught southern black rhinoceros, immobilized to facilitate collection of 6.0 L of blood (PCV = 54%) into ACD bottles (anticoagulant citrate dextrose solution, The Metrix Company, Dubuque, Iowa 52002, USA). The rhinoceros calf, with ongoing nasal hemorrhage, was sedated with butorphanol tartrate (Torbugesic, Fort Dodge Animal Health, Fort Dodge, Iowa 50501, USA; 30 mg i.v.). Within 2 hr of collection and without prior cross match, a whole blood transfusion was administered, raising the calf's PCV from 9% to 18%. After the transfusion, and for the first time since diagnosis of ALL, no lymphoblasts were identifiable in the rhinoceros's peripheral blood smear.

By day 30, the WBC reached a nadir of 1,250/μl, and the estimated platelet count was 71,000/μl. The calf was given filgrastim, a recombinant human granulocyte colony-stimulating factor (G-CSF; Neupogen, Amgen Inc., Thousand Oaks, California 91320, USA; 5,000 μg/1 mL s.c.d.) for 3 days. On day 31, approximately 20 hr after the first G-CSF dose, there was a fivefold increase in WBC to 6,450/μl and a decline in PCV to 14%. After the second G-CSF dose on day 32, WBC increased from 6,150 to 8,750/μl, and after the third dose, a further increase was observed to 15,250/μl on day 33. Biopsy of an emerging skin nodule from the calf's left shoulder revealed a number of pigmented dematiaceous hyphae consistent with phaeohyphomycosis. On day 36, declines in both PCV (11%) and WBC (12,825/μl) were noted, with a reduction in bands to 2%. A coagulation panel revealed a slight prolongation in prothrombin time (13.4 sec) and normal levels of antithrombin III (143%) compared with equine values (Texas A&M College of Veterinary Medicine, ref. ranges: PT = 9.0–10.8 sec, ATIII = 108–208%). By day 37, the calf was severely depressed with very pale mucous membranes, increased respiratory rate, and mandibular edema. A major and minor cross-match was performed on blood collected 24 hr previously from a female southern black rhinoceros housed at a nearby facility. No incompatibility was found, and 2 L of whole blood was warmed and given via slow i.v. infusion. After the transfusion, the PCV rose from 5% to 6% and peripheral lymphoblasts were absent in the blood. The heart rate was elevated throughout the transfusion, but the respiratory rate remained within normal limits. Three hours after the transfusion was completed, the calf died acutely with no clinical or pathologic indication of a transfusion-related complication.

The proximate cause of death was congestive heart failure. On necropsy, there was prominent gross evidence of both severe acute and chronic passive congestion of the lungs, liver, and spleen. Histologically, there was marked pulmonary edema, often with intra-alveolar hemorrhage, and extensive interstitial hemosiderosis but no pneumonic or leukemic infiltrates. There was patchy interstitial myocardial edema and generalized degenerative change, including multifocal perinuclear vacuolization, rare focal myocytolysis with inflammatory cell aggregates, and rare but wide-scattered dystrophic iron-positive granular deposits within myocardial fibers. Myocardial lesions were consistent with cytotoxic changes ascribed to doxorubicin-induced cardiomyopathy in humans.[2] Moderate hemosiderosis was also observed in the spleen, liver, multiple lymph nodes, and duodenal villi. Microscopically, bone marrow morphology was normal with no clear evidence of leukemic infiltrates in the marrow or any other tissue.

DISCUSSION

Although clinical management of ALL in this rhinoceros was based on previous human and animal studies, treatment of a semiwild animal provided unique challenges. There was limited ability to monitor serial changes in the centers of hematopoiesis. There was also minimal ability to control exposure of this immunocompromised patient to pathogens in the environment.[3] The possible responses of this species to chemotherapeutic drugs were also unknown. Decisions were made with a paucity of information regarding rhinoceros hematology, physiology, and pharmacology.[4,5] The conditioning process of black rhinos at this facility was a key factor in management of multiagent che-

motherapy in a species such as the rhinoceros. Black rhinoceroses are conditioned with a positive food reward to stand readily for routine venipuncture. This process facilitated treatment and allowed for serial sedation that was needed for such invasive procedures as catheterization and blood transfusion.[24]

The chemotherapeutic induction protocol and dosage schedule were empiric, based on experience with domestic animals.[2,6] The antimetabolite cytarabine may have been ineffective in this case for reasons including poor cellular uptake, detoxification by cytidine deaminase, deletion of the activating enzyme, altered DNA affinity, or high levels of the competing normal metabolite.[2] Comparative studies of erythrocyte metabolism have revealed major differences between rhinoceroses and other mammals.[17,19,22] These metabolic differences may be reflected in other tissues as well, making tenuous any therapeutic approach that relied principally on host cell metabolism.[20] The alkylating agent cyclophosphamide initially resulted in marked clinical improvement and decreased lymphoblast numbers, but subsequent use resulted in only transiently reduced circulating lymphoblast numbers. Such habituation of response may have been due to inherent resistance in a subset of leukemic cells, and rapid return of leukemic cells after an initially positive response to cyclophosphamide induction is common with human leukemias (Territo, pers. comm.). Initial vincristine therapy was also followed by marked clinical improvement and reduced lymphoblast numbers, but response was marginal after subsequent administration. This may have been related to either resistance or dose-dependent factors.

Administration of doxorubicin resulted in markedly decreased peripheral leukocyte numbers. Doxorubicin is a very effective agent for the treatment of lymphoid neoplastic diseases in domestic animals,[2] and it is the anthracycline most commonly used against human hematologic malignancies, including ALL.[32] In human erythrocytes, doxorubicin semiquinone produces hydroxyl radicals by direct reduction of H_2O_2.[4] Free radical formation adds to the antitumor activity but also produces the dose-limiting cardiotoxicity of anthracyclines.[12,29,31] The enzyme catalase, one of the primary mechanisms responsible for removing H_2O_2-induced free radicals, has reduced activity in rhinoceros erythrocytes relative to humans and other mammals, and in black rhinoceroses particularly.[17,20] In addition, domestic animal cardiomyocytes demonstrate very low levels of catalase activity compared with other cell types.[9] Iron overload may have compounded the problem in this calf because doxorubicin avidly combines with iron to generate highly damaging hydroxyl free radicals in coupled redox reactions with hydrogen peroxide.[30,29] The cardiac histologic lesions in this case may be a morphologic reflection of an inordinate sensitivity to reactive oxygen species postulated for rhinoceros tissues beyond the erythrocyte.[20,31] Considering the enhanced effects of doxorubicin in the presence of high iron, perhaps concomitant iron chelation therapy in this case may have limited the cardiotoxic effects of the anthracycline.

Anemia was a major complicating factor in this case. In humans with leukemia, unresolved infection in the pancytopenic patient is strongly correlated with terminal hemorrhage, with a 12–20% death rate attributed to the synergistic effects of infection and hemorrhage.[12,16] Although infection, hemorrhage, and anemia were major complications, histologic evidence of doxorubicin cardiotoxicity at a relatively low dosage suggests that this cardiotoxicity may have been the proximate cause of death, responsible for the severe congestive heart failure that was prominent at necropsy.

An important component for management of childhood ALL is the ability to prognosticate and thereby apply a risk-oriented therapeutic approach based on extensive clinical trials.[14,27,33] Similar information is obviously lacking for rhinoceroses, resulting in inexact extrapolation of knowledge from other species. Because of the black rhinoceros' inordinate sensitivity to oxidants, disease management in this species requires careful consideration of the pharmacology of all drugs selected for treatment.

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HALICEPHALOBUS GINGIVALIS (NEMATODA) INFECTION IN A GREVY'S ZEBRA (*EQUUS GREVYI*)

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Abstract: A 6-yr-old female Grevy's zebra (*Equus grevyi*) with a disseminated rhabditiform nematode infection is described. Antemortem clinical signs were limited to blindness and abnormal behavior believed to be caused by a recurrent nematode-induced uveitis. Histologic examination of the kidneys, heart, eyes, uterus, and lymph nodes revealed granulomas containing multiple sections of rhabditiform nematodes. Most of the recovered nematodes were larval stages with only a few adult females noted. The adults measured 243–297 μm × 11–16 μm ($\bar{x}$ = 269 × 14 μm). The distinctive rhabditiform esophagi had corpus : isthmus : bulb proportions of 19:11:5. On the basis of adult morphology, the nematode was identified as *Halicephalobus gingivalis*. This is the first report of this parasite in a zebra and indicates that this parasitic granulomatous disease should be considered in zebras with neurologic disease.
Key words: Grevy's zebra, *Equus grevyi*, *Halicephalobus gingivalis*, Nematoda, parasite, uveitis.

INTRODUCTION

The nematode *Halicephalobus* (*Rhabditis*) *gingivalis* was first described by Stefanski from the gingiva of a horse.[18] It has subsequently been reported from nasal or gingival tissues, kidneys, lungs, brain, spinal cord, bone, mammary gland, prostate gland, and adrenal glands of more than 30 horses.[illegible] Rhabditiform nematode infections in horses are rare but widespread geographically, with cases reported from the United States, Canada, the United Kingdom, The Netherlands, Poland, Japan, Switzerland, Colombia, and Egypt.[illegible]

Halicephalobus gingivalis is classified in the order Rhabditida and is probably a facultative saprophyte that is usually associated with decaying plant material.[illegible] In infected tissues, only the adult females, larval stages, and eggs have been identified, suggesting that reproduction may be parthenogenic.[illegible] The genus *Halicephalobus* was originally named *Rhabditis* and then renamed *Micronema*.[illegible] It was recently determined that *Halicephalobus deletrix*, *Micronema deletrix*, *Trilabiatus gingivalis*, *Tricephalobus gingivalis*, *Rhabditis gingivalis*, and *H. gingivalis* are synonymous species, all properly referred to as *H. gingivalis*.[illegible] This is the first published report of *H. gingivalis* infecting a zebra. The clinical and pathologic features resemble those in previous reports of infections in horses, with wide dissemination in multiple tissues.[illegible]

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CASE REPORT

A 6-yr-old female Grevy's zebra (*Equus grevyi*) developed intermittent neurologic signs, including blindness. The zebra had never been away from its place of birth in northeastern Florida. It was housed with an apparently healthy breeding herd of 11 zebras in a 2.4-ha Bermuda grass pasture. The enclosure was mowed routinely, and the manure was dispersed occasionally into the grass by dragging the field. Although the enclosure was adjacent to a large domestic horse breeding facility, the zebras had no direct contact with horses nor was their enclosure ever used to graze horses.

Routine preventative care for the zebras consisted of periodic immobilization for hoof trimming, physical examination, and annual vaccination, which included tetanus toxoid, eastern equine encephalitis, western equine encephalitis, and influenza (Fluvac EWT, Fort Dodge Laboratories, Inc., Fort Dodge, Iowa 50501, USA) and equine rhinopneumonitis (Pneumabort K, Fort Dodge Laboratories, Inc.) At approximately 2-mo intervals, the herd was given fenbendazole (Hoechst Roussel Agri Vet Co., Somerville, New Jersey 08876, USA) at dosage of 8 mg/kg in the feed.

One month prior to the onset of clinical signs, the mare delivered a normal foal without assistance. The mare's clinical signs began as intermittent abnormal behavior observed while it was in the enclosure with its foal. During these episodes, the mare would walk in wide circles to the left, with its head slightly down. Blindness was suspected because the animal would occasionally walk into cor-