MEDICAL MANAGEMENT OF RECURRENT EOSINOPHILIC GRANULOMA IN TWO BLACK RHINOCEROS (DICEROS BICORNS)


Abstract: Recurrent eosinophilic granuloma (EG) in two captive eastern black rhinoceros (Diceros bicornis michaeli) was effectively managed with glucocorticoids and antihistamines. The first case was a female and the second case was a male. The animals were housed at separate institutions and initially presented with hemorrhagic oral lesions. Multifocal lesions occurred in the second case. Multiple biopsies were taken from each animal, all of which were consistent with EG. Each animal was anesthetized multiple times for surgical treatment but experienced frequent recurrence. Due to lack of response to therapy and the risks and adverse events associated with repeated anesthesia, medical treatment was initiated in both cases using a tapering dose of oral dexamethasone. The lesions dramatically improved, but would recur frequently after treatment. Hydroxyzine, an oral antihistamine, greatly reduced the incidence and severity of the lesions. Medical management with glucocorticoids and antihistamines minimized stressful anesthetic events in both cases and contributed to the successful management of this recurrent disease. The exact pathogenesis of EG in black rhinoceros remains unknown but response to antihistamines suggests an allergic etiology.

Key Words: Allergy, black rhinoceros, dexamethasone, Diceros bicornis, eosinophilic granuloma, hydroxyzine

INTRODUCTION

Eosinophilic granuloma (EG) affects a variety of mammalian species, including horses,17,23 domestic and nondomestic cats,8,20 dogs,2,16,21 and captive black rhinoceros,14 and typically manifests in oral or cutaneous sites. While the exact etiology of EG is unknown, in all species hypersensitivity reactions are considered the primary cause.3,8,17,14,16,23 In horses, a hypersensitivity to insect bites has been proposed as the mostly likely etiology.19 Hypersensitivity to silicone coating on hypodermic needles has been demonstrated.19 Infectious, hereditary, and traumatic etiologies have also been proposed.3,17 In domestic species, treatments have included surgical excision, laser therapy, cryotherapy, and immune modulators such as glucocorticoids, cyclosporine, and antihistamines.3,8,17,23 Both intralesional and systemic glucocorticoids have been effective treatments in horses.15,17

EG is one of several dermatological diseases of captive black rhinoceros.14 Skin disease in general is a major cause of morbidity and occasionally mortality in captive populations of this species.4 The most common condition is a condition similar to superficial necrolytic dermatitis (SND),4 although the pathophysiology may differ from SND reported in dogs.4 EG is a less common condition that may resemble SND grossly but is distinct histologically.14 Although EG lesions often resolve spontaneously in black rhinoceros,14 chronic and recurrent cases are recognized and present a therapeutic challenge in this charismatic and highly endangered species. Chemical immobilization is generally necessary for close examination, biopsy, and surgical treatment of black rhinoceros. Anesthesia has inherent risks and requires a large investment of time, money, facilities, equipment, and experienced personnel. Cryotherapy and glucocorticoids are treatment modalities that have been used to treat EG in black rhinoceros,10,13,14 but there are no published recommended protocols. Additionally, there are concerns over possible associations between sys-
tic glucocorticoid therapy and fungal pneumonia in this species.9,14

This report describes the safe and effective medical management of EG in two black rhinoceros at different facilities. In both cases, EG lesions were chronic and recurrent, and various treatments were attempted unsuccessfully before glucocorticoids were used and proved highly effective. Antihistamines were later added to the protocol, which decreased the intensity and frequency of recurrence of EG lesions in both animals. These examples suggest that antihistamines and glucocorticoid therapy may effectively modulate the clinical course of EG in black rhinoceros.

CASE REPORT

Case 1

A 7-yr-old breeding female eastern black rhinoceros (Biceros dicorns michaelii) presented in March 2000 with bleeding from the mouth. A unilateral, raised, proliferative, ulcerated and intermittently hemorrhagic lesion of the maxillary buccal mucosa was found. The animal was born at and kept in a 6-acre grass paddock at Port Lympne Wild Animal Park in Kent, England (51°4′39.345″N, 1°0′4.68″W) as part of a breeding herd of 14 black rhinoceros. The diet consisted of a mix of browse, alfalfa hay, low-iron rhinoceros pellet, and fresh produce.

Seven days after initial presentation, the animal was anesthetized by remotely delivered (Daninject ApS, Sellerup skove 116, DK 7080, Borkop, Denmark) etorphine and acepromazine (Immobilon, etorphine 2.45 mg/ml and acepromazine 10 mg/ml, Novartis Animal Health UK Ltd., New Cambridge House, Litlington, Nr Royston, Herts, SG8 0SS, UK; 1.5 μg/kg etorphine and 6 μg/kg acepromazine i.m.) and placed in lateral recumbency. Values for complete blood count and serum biochemistry were within the reference range (ISIS Physiological Data Reference Values, 2001 ed., Apple Valley, Minnesota 55124, USA). On oral examination, an ulcerated, 10 × 4 × 2-cm, raised lesion with irregular edges was noted on the buccal mucosa of the left side of the upper lip. wedge biopsies of the lesion were taken and placed in formalin for histopathology. Anesthesia was reversed using diprenorphine (Revivon, 3.26 mg/ml, Novartis Animal Health UK Ltd.; 2 μg/kg i.v.) Recovery was smooth, with no clinical complications noted during or after the procedure. All successive immobilizations in this case were performed with a similar protocol and without complications.

Initial histopathology revealed a hyperplastic epithelium and submucosal inflammation associated with many eosinophils, consistent with EG in the black rhinoceros. The animal was anesthetized 7 days later for additional treatment and to further investigate the nature of the lesion. Cryosurgery with liquid nitrogen was used on the ulcerated area using custom-made brass tools. The tools were dipped in liquid nitrogen and applied to the lesion for 15 sec, then allowed to thaw for 3 min in three freeze-thaw cycles. Over the next several days, the lesion regressed but did not resolve. The animal was anesthetized again 11 days later and cryosurgery was repeated. The lesion was considered fully resolved 1 mo later. Nine days later, however, bleeding was noted from the animal's mouth, and another oral lesion was treated with cryosurgery under anesthesia. During the next 8 mo the lesion returned three additional times and the animal was anesthetized each time for cryosurgery. During the third sedation further biopsies were taken and placed in formalin. Histopathology again confirmed the lesion as being consistent with EG.

Due to the rapid recurrence of the lesion after each surgery the decision was made to convert to medical therapy with oral dexamethasone (2-mg tablets, TioFarma BV, Benjamin Franklinstraat 9, Oud-Beijerland, The Netherlands). A tapering dose was administered (initial dose of 0.1 mg/kg p.o. s.i.d. × 3 days, then 0.08 mg/kg p.o. s.i.d. × 3 days, then 0.06 mg/kg p.o. s.i.d. × 3 days, then 0.04 mg/kg p.o. s.i.d. × 3 days, then 0.02 mg/kg p.o. s.i.d. × 3 days). All oral medications were provided in preferred food items.

Clinical improvement of the EG was evident within 24 hr, and near complete resolution was achieved within 8 days of initiating dexamethasone. On visual examination 2 wk after completion of the dexamethasone treatment, the lesion was fully resolved. No adverse effects from the dexamethasone were noted.

Seven weeks later, a similar lesion appeared in the oral cavity. Oral dexamethasone was administered as previously described. Clinical improvement began within 24 hr and the lesion was fully resolved within 1 wk.

Over the next 10 years, nine lesions occurred at various anatomical regions and were confirmed as EG by histology or cytology. Each episode was treated with oral dexamethasone using the same dose and schedule as previously described, with clinical resolution within 3–5 days. No adverse
effects to the dexamethasone were observed, and patient compliance was excellent. The animal has given birth to a female infant since developing EG lesions.

In an attempt to decrease recurrence rate, treatment with an oral antihistamine (Atarax, hydroxyzine hydrochloride 10-mg tablets; Alliance Pharmaceuticals Ltd., Chippenham, SN15 2BB, UK) was initiated after a consultation with one of the authors (JRZ). The dose was slowly increased over several days (0.50 mg/kg p.o. b.i.d. × 3 days, then 0.75 mg/kg p.o. b.i.d. for 3 days, then 1 mg/kg p.o. b.i.d. continuously) to avoid causing sedation. Compliance was excellent and no behavioral changes were noted. Treatment continued for 6 mo. During this period no EG lesions were noted. Due to the relative infrequency of lesion recurrence, ongoing treatment with antihistamines was stopped, and no further EG lesions have been noted since.

Case 2

A 7.5-yr-old, 1,050-kg breeding male eastern black rhinoceros (Biceros dicornis michaeli) was presented in September 2004 with decreased appetite and a unilateral, raised, ulcerated, and intermittently hemorrhagic lesion of the maxillary buccal mucosa. The animal was hand-raised and housed in a 2-acre, outdoor dirt yard exhibit at the San Diego Zoo Safari Park (33°5′57.8682″N, 116°59′59.8488″W), with two other clinically unaffected black rhinoceros. The diet consisted of mixed hay, high fiber herbivore pellet (San Diego Zoo Global High Fiber ADF 25 pellet 1/2″, Western Milling, Goshen, California 93227, USA), fresh produce (e.g., apples, lettuce), and browse items (primarily Acacia saligna, as well as Ficus rubiginosa or Ficus microcarpa).

Ten days after initial presentation, the animal was anesthetized by remotely delivered (Telinject USA, Inc., Agua Dulce, California 91390, USA) carfentanil citrate (Wildnil®, 3 mg/ml, ZooPharm, Laramie, Wyoming 82070, USA; 1 μg/kg i.m.) and placed in 30-degree sternolateral recumbency. Supplemental oxygen was delivered via nasal insufflation at a rate of approximately 15 L/min. Clinical monitoring included pulse oximetry, capnography, and intermittent blood gas analysis. Values for complete blood count and serum biochemistry were within the reference range (ISIS Physiological Data Reference Values, 2001 ed.), with the exception of a marginally increased hematocrit. This was presumed to be from dehydration secondary to preanesthetic fasting. Fungal antibody titers were submitted, which were negative for Aspergillus spp. The titers were weakly positive for Coccidioides immitis, and remained so during subsequent episodes, suggesting prior exposure as per the reference laboratory (Coccidiomycosis Serology Lab, University of California, Davis, Davis, California 95616, USA).

On oral examination, an ulcerated, 10 × 5 × 4-cm lesion with irregular edges was noted on the labial mucosa of the left side of the upper lip. Wedge biopsies of the lesion were taken, submitted for bacterial and fungal culture, and placed in formalin for histopathology. Anesthesia was reversed using naltrexone HCl (50 mg/ml, Komoto Custom Care Pharmacy, Bakersfield, California 93301, USA; 0.1 mg/kg i.v., 0.1 mg/kg i.m.). Recovery was smooth, with no clinical complications noted during or after the procedure. All successive immobilizations in this case were performed with a similar protocol and without complications.

Histopathology revealed marked epithelial hyperplasia and ulceration, and the submucosa was expanded by granulation tissue and inflammatory cell infiltrates. Inflammatory cells were predominantly eosinophils with fewer lymphocytes, macrophages, and neutrophils. Histopathologic findings were consistent with eosinophilic granuloma of black rhinoceros. Aerobic culture of the lesion yielded a moderate growth of nonhemolytic Staphylococcus sp., alpha-Streptococcus sp., and gamma-Streptococcus sp. Fungal and anaerobic cultures were negative.

The animal was anesthetized 11 days later for additional treatment and to further investigate the nature of the lesion. Additional biopsies were taken, and cryotherapy with liquid nitrogen was used on the ulcerated area using brass tools custom-made for various-sized lesions. These flat-surfaced tools were dipped in liquid nitrogen and applied to the lesion for 15 sec. The lesion was then allowed to thaw for 3 min. A total of three freeze-thaw cycles were repeated. Over the next several days, the lesion regressed and was considered fully resolved within 3 wk. Histologic interpretation was again consistent with a diagnosis of EG of black rhinoceros.

No additional treatment was necessary, and there were no further clinically apparent EG lesions for the next 1.5 yr. At that time the animal developed a mildly hemorrhagic, ulcerated, proliferative, and raised 13 × 4 × 1-cm lesion at the cranial edge of the base of the prepuceal skin (Fig. 1). The animal was anesthetized 3 wk later and biopsies confirmed the prepuceal lesion as an EG. Daily topical treatment was instituted with 2%
chlorhexidine solution (Phoenix Pharmaceutical, Inc, Saint Joseph, Missouri 64507, USA). The lesion regressed slowly and resolved over 3 mo. Over the next year, lesions at similar locations on the prepuce occurred four times, had an average duration of 42 days, and were treated topically with a combination of dilute chlorhexidine solution, an ointment containing nystatin, neomycin, thiostrepton, and triamcinolone (Entederm Ointment, Vet One, Meridan, Idaho 83660, USA), and a commercially available fly repellent (Repel-X®p, 0.4% pyrethrin, Farnam Companies, Inc., Phoenix, Arizona 85013, USA).

Three years after initial presentation, the animal developed an ulcerated, intermittently hemorrhagic, raised, 5 × 3 × 3-cm lesion in the left naris, occluding approximately 90% of the nasal opening. Wedge biopsies obtained under anesthesia were consistent with EG, this time with focal areas of collagen surrounded by degranulated eosinophils known as flame figures1,6 (Fig. 2). Because the lesion persisted for several weeks, the animal was anesthetized for treatment with intralesional triamcinolone acetonide (10 mg, Kenalog®, 10 mg/ml, Bristol-Myers Squibb Co., Princeton, New Jersey 08543, USA). The drug was injected in a fan-like pattern at the base of the lesions using a 20-ga needle. The epistaxis and stridor fully resolved within 1 wk.

After the initial episodes, additional EG lesions occurred periodically over the next year. The lesions occurred in previously affected anatomical regions, including the cranial aspect of the base of the prepuce, and the buccal and nasal mucosa. The animal was anesthetized nine additional times for treatment of the lesions. All biopsies of the lesions obtained during four of the subsequent anesthetic events were histologically confirmed as EG. The average clinical duration of these lesions during this period was 3 mo with an average interval between episodes of 8 days. The last episode during this period included a single nasal lesion that caused intermittent epistaxis for approximately 6 mo despite eight attempts at multimodal surgical treatment under general anesthesia as described previously.

During the increasingly frequent immobilizations for treatment, the animal exhibited more vocalizations and antisocial behavior, both of which were unusual for this generally tractable, hand-raised rhinoceros. Because of these marked signs of stress, and after consultation with one of the authors (JH), the decision was made to convert to medical therapy with oral dexamethasone (4-mg tablets, PAR Pharmaceutical Companies, Inc., Spring Valley, New York 10977, USA). A 12-day tapering dose was administered (initial dose of 0.1 mg/kg p.o. s.i.d. × 3 days, then 0.075

Figure 1. Black rhinoceros, case 1, raised, ulcerated, and hemorrhagic mass at base of prepuce skin. This lesion was histologically confirmed as an eosinophilic granuloma.

Figure 2. Black rhinoceros, case 1, nasal eosinophilic granuloma. A. There is marked epithelial hyperplasia overlying a hypercellular submucosa composed of granulation tissue and inflammatory cell infiltrates. Bar = 300 μm. B. Inflammatory cells are predominantly eosinophils. Bar = 15 μm. C. A flame figure composed of a coagulum of degranulated eosinophils surrounded by macrophages including multinucleated giant cells (arrow). Bar = 30 μm. H&E stain.
mg/kg p.o. s.i.d. × 3 days, then 0.05 mg/kg p.o. s.i.d. × 3 days, then 0.025 mg/kg p.o. s.i.d. × 3 days). Due to the concerns for systemic glucocorticoids precipitating fungal pneumonia in this species, prophylactic voriconazole (USP powder 1 mg voriconazole/1 mg dry weight product, Pfizer, Inc., New York, New York 10017, USA; 7 mg/kg p.o. s.i.d. 17 days) was initiated 3 days prior to the dexamethasone. All oral medications were provided in preferred food items. During therapy, voriconazole was suspected of causing gastrointestinal upset in the animal, and was therefore discontinued after 17 days, with a subsequent improvement in appetite and attitude over the following several days.

Clinical improvement of the EG was evident within 24 hr of initiating dexamethasone therapy, and near complete resolution was achieved within 4 days. No adverse effects other than those attributable to the voriconazole were noted. Despite positive response to symptomatic treatment, over the next 15 mo, lesions frequently occurred, either at the base of the prepuce (n = 8) or the oral cavity (n = 7). Eight of these episodes required treatment with oral glucocorticoids using the same dose and schedule each time, and resolution was noted within 3–5 days after initiating therapy. No adverse effects to the dexamethasone were observed.

Based on this extremely high recurrence rate, an oral antihistamine (hydroxyzine pamoate, 50 mg capsules; Patheon Pharmaceutical, Inc, Cincinnati, Ohio 45232, USA) used in the successful treatment of EG in horses (Rosychuk, pers. comm.) was initiated in this black rhinoceros. The hydroxyzine dose was slowly increased over several days (0.50 mg/kg p.o. b.i.d. × 3 days, then 0.75 mg/kg p.o. b.i.d. for 3 days, then 1 mg/kg p.o. b.i.d. continuously) to avoid the potential sedative properties of this medication. Compliance was excellent and no changes in mentation were noted.

For the next 5 mo, only two minor lesions on the preputial skin were noted, and neither required treatment. No clinically apparent lesions occurred in the oral or nasal cavities. Due to the dramatic decrease in EG lesions, hydroxyzine was discontinued. Three weeks later an oral lesion appeared, and was treated successfully with oral dexamethasone as previously described.

Oral hydroxyzine (1 mg/kg p.o. b.i.d.) was reinstituted, and was continuous until the completion of this case report (a period of 21 mo). Seven lesions have occurred, all affecting the base of the prepuce. Only two of these were considered clinically significant based on size, hemorrhage, and apparent discomfort, and both were successfully treated with oral dexamethasone. Since medical management of the EG lesions was started, the animal’s calm demeanor and tractability has returned to normal, and he has sired three healthy calves.

**DISCUSSION**

Eosinophilic granuloma is one of a number of diseases of captive black rhinoceroses. Skin disorders in particular affect a large proportion of the ex situ population. A condition grossly similar to superficial necrolytic dermatitis (SND) of dogs is the most common condition in black rhinoceroses. Although SND and EG can cause grossly similar lesions, their anatomic distribution and histological appearance are distinct enough to categorize them as separate disease processes.

The etiology and pathogenesis of EG in all species are unknown, although underlying hypersensitivities are strongly suspected. In domestic species, insect bite hypersensitivity, atopic dermatitis, food allergies, microtrauma, autoimmune and infectious diseases have all been suggested as potential underlying causes. The gross appearance and anatomical location may vary between species, but EG lesions have common histopathologic features in all species. Spontaneous resolution and recurrence are common features in most species, although they may persist in horses.

The histopathologic features of EG in all species are epidermal hyperplasia, erosion or ulceration, and prominent infiltrates of eosinophils and other inflammatory cells within the submucosa or dermis. Flame figures, a term used to describe focal areas of collagen surrounded by degranulated eosinophils, are variably seen. Although not every lesion in these cases was examined histologically, multiple biopsies were obtained during the treatment period for each animal and all were consistent with EG, including the variable presence of flame figures.

Diagnosis of EG is often presumptive based on clinical features and gross appearance; however, definitive diagnosis requires histopathology. Hematological and biochemical values are generally unremarkable. Infectious agents have been considered, and in the first case, bacterial cultures from biopsy sites did yield a mixed bacterial growth. However, in EG lesions, ulceration often allows secondary bacterial colonization. Although allergens are suspected to be the underly-
The clinical response to dexamethasone was dramatic. Before glucocorticoid therapy, each episode’s average duration was 76 days and often included multiple immobilizations for treatment. After initiating dexamethasone, each episode lasted an average of 4 days, and was usually considered resolved within 24 hr. Despite success in rapid symptomatic resolution of EG lesions, steroids failed to provide long-term resolution. The lesions recurred frequently in both cases, likely because steroid treatment did not appear to address the underlying cause. Recurrence is a variable feature of EG in other species, and has been reported in black rhinoceros for periods of several years.

Because the underlying etiology of EG in most species is suspected to be hypersensitivity to an unidentified allergen, the therapy was modified to address this component. Antihistamines are often utilized in allergic diseases of domestic animals, and the H1-receptor antagonist hydroxyzine has been associated with the highest degree of success in the management of allergic skin disease in horses. Adverse effects in horses are rare and most commonly manifest as sedation, lethargy, and behavioral changes. To the authors’ knowledge, this is the first reported use of hydroxyzine in black rhinoceros. No adverse effects were appreciated in either of these cases. Hydroxyzine appears safe when given at the prescribed dose (1 mg/kg p.o. b.i.d.).

After the initiation of antihistamine therapy, the frequency of clinically significant EG lesions was dramatically reduced in case 2. The apparent clinical resolution of the lesions on continuous antihistamine therapy in this case supports the concept that an allergen or allergens may play a role in the etiology of the disease. Interestingly, during a period of approximately 10 wk when hydroxyzine was discontinued, two oral lesions appeared and required short courses of dexamethasone to resolve. No oral or nasal lesions occurred in over 3 yr while this animal was being treated with hydroxyzine continuously. The first case had no episodes of EG during continuous hydroxyzine therapy, however, the recurrence rate was considered too low to justify treatment and it was therefore discontinued. The low recurrence rate in case 1 also makes it impossible to conclusively evaluate the effects of hydroxyzine in prevention of recurrence.

Short-term anti-inflammatory doses of glucocorticoids and continuous long-term use of antihistamines was safe and effective for treatment of
EG in the two animals in this case report. No complications, including fungal pneumonia, were encountered from short-term low dose glucocorticoid therapy in these cases. The addition of hydroxyzine to the treatment protocol significantly reduced the recurrence rate and severity of the EG lesions.

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LITERATURE CITED


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