ORAL, NASAL, AND CUTANEOUS EOSINOPHILIC GRANULOMAS IN THE BLACK RHINOCEROS (DICEROS BICORNIS): A LESION DISTINCT FROM SUPERFICIAL NECROLYTIC DERMATITIS


Abstract: Oral, nasal, and cutaneous lesions resembling eosinophilic granulomas (EGs) were observed in eight captive black rhinoceroses (Diceros bicornis). Oral lesions were observed in all affected animals and occurred most often behind the prehensile lip. The typical clinical history of affected animals included oral bleeding or epistaxis from multilobulated, fungating, proliferative masses with areas of ulceration. Histologically, lesions were characterized by prominent infiltrates of eosinophils and rare foci of collagen degeneration on a background of marked submucosal or dermal neovascularization. Mucosal or epidermal hyperplasia was also present sometimes in association with distinctive epithelial degenerative changes consistent with superficial necrolytic dermatopathy of black rhinoceroses. Lesions of EG and superficial necrolytic dermatopathy were interpreted as being concurrently manifested in these cases. EG lesions spontaneously resolved over periods of 30 days–7 mo and were recurrent in three animals. Lesions were responsive to treatment with corticosteroids or to local cryotherapy with liquid nitrogen. Two animals treated with systemic corticosteroids died of disseminated fungal infections, emphasizing that corticosteroids should be used cautiously in black rhinoceroses.

Key words: Black rhinoceros, Diceros bicornis, eosinophilic granuloma, superficial necrolytic dermatitis, ulcerative dermatopathy.

INTRODUCTION

A vesicular and ulcerative disease of the skin and mucous membranes that clinically and histologically resembles superficial necrolytic dermatitis (SND) in dogs and necrolytic migratory exanthema (NME) in humans has been described as a major cause of morbidity in captive black rhinoceroses (Diceros bicornis). Histologic lesions typical of SND in black rhinoceroses include epidermal hyperplasia, laminar intercellular edema, hydropic degeneration of keratinocytes, and parakeratosis. Inflammatory cell infiltrates have not been described as a prominent feature of SND or NME; however, a small subset of black rhinoceroses with SND was noted to have prominent eosinophilic inflammatory infiltrates and areas of collagen degeneration in addition to a spectrum of epithelial changes attributed to SND. The histologic appearance of the inflammatory lesions in these animals strongly resembles the cutaneous or oral mucosal eosinophilic granulomas (EG) of domestic animals. EG are characterized by eosinophilic inflammation, foci of collagen degeneration with associated granulomatous inflammation, epithelial hyperplasia, and ulceration and have been described most frequently in cats, with similar lesions also being observed in dogs and horses. We review oral, nasal, and cutaneous lesions in black rhinoceroses that clinically and histologically resemble EG and suggest that EG in black rhinoceroses is a distinct lesion that in some instances is concurrently manifested with epithelial changes typical of SND.

MATERIALS AND METHODS

Study population and clinical findings

Eight captive black rhinoceroses that had lesions suggestive of EG were identified from seven different zoological parks in the United States with subsequent review of the clinical, gross, and histologic findings as well as treatment outcome. Six affected animals were from a database of black rhinoceroses with cutaneous, oral, or nasal mucosal ulcerative lesions used to characterize the SND syndrome. Two cases were identified through pathology submissions to one of the authors (LM) as part of ongoing SND research or from the pathology records of the Zoological Society of San Diego. Medical records, pathology reports, and histologic sections (when available) from these cases were ob-
tained under the auspices of the Black Rhinoceros Species Survival Plan as described previously. The six animals identified in the SND database had previously been incorporated in a published report describing the spectrum of lesions observed with SND, and two of these were earlier reported in a professional proceedings.

**Histology**

In all cases, tissues were processed routinely for histology and sections stained with hematoxylin and eosin. Selected sections were also stained with Gomori’s methenamine silver (GMS), Warthin-Starry (WS), and toluidine blue. Original histologic sections or paraffin blocks were available for review in six cases with only histopathology reports available for two cases.

**RESULTS**

**Study population and clinical findings**

Black rhinoceroses with EG were all of the Eastern subspecies (*Diceros bicornis michaeli*) and were 7–29 yr of age at the time of the first histologically confirmed eosinophilic inflammatory lesion. Six animals were female and two were male. Four animals were wild caught, and four were captive born. All eight rhinoceroses had lesions within the oral cavity, three of eight had lesions within the nasal cavity, and two of eight had cutaneous lesions. Although simultaneous oral and nasal lesions occurred in three of eight animals and simultaneous oral and cutaneous lesions occurred in one animal, others had a single EG lesion at any one time. Three of the eight animals had recurrent and histologically confirmed EG lesions occurring over periods of several years. Other animals had recurrent oral or cutaneous ulcerative lesions that were not histologically evaluated, and it is not known whether these lesions represented EG lesions or were part of the SND syndrome, which had also been diagnosed histologically (without evidence of eosinophilic inflammation) in several of these animals. No apparent seasonality to the development of lesions was noted. Using studbook records, it was determined that none of the captive born animals had parents in common.

Animals with nasal or oral lesions usually were presented with a history of epistaxis or of bleeding from the mouth but were otherwise asymptomatic. One animal with an oral lesion was noted to repeatedly rub the affected area against exhibit fixtures. Oral lesions were multilobulated, fungating proliferative masses, 4–10 cm in greatest dimension with multifocal areas of ulceration (Fig. 1). In six of eight animals, oral lesions were located on the rostral upper lip (immediately behind the prehensile or “hook” lip), in two of eight were on the lower lip, and in one animal, the hard palate. Nasal lesions occurred on the external nares, were grossly similar to the oral lesions, and measured up to 10 cm in greatest dimension. Cutaneous lesions were asymptomatic and presented as single nodules, 2–7 cm in diameter with evidence of ulceration. These lesions were present on the skin of the hip in one animal and on the supramammary skin and external ear (pinna) of a second animal.

Three affected animals were treated with systemic prednisolone (dose range: 100 mg–1 g, p.o., s.i.d.) with subsequent clinical resolution of the lesions. Two corticosteroid-treated animals, however, died of systemic zygomycosis within 1 mo of initiation of therapy. Nasal and oral lesions in two animals were successfully treated with localized cryotherapy using topical application of liquid nitrogen. Lesions in all other animals resolved spontaneously in as little as 30 days to as long as 7 mo after clinical recognition.

**Histologic findings**

The oral, nasal, and cutaneous lesions were all histologically similar and consisted of highly cellular foci that expanded the superficial to middermis or submucosa. A single cutaneous lesion was limited to the superficial dermis at a focus of epidermal ulceration. In all cases, underlying both ulcerated and intact epithelium, there were infiltrates of moderate to high numbers of eosinophils with fewer neutrophils and occasional macrophages (Figs. 2, 3). In some areas, neutrophils were the predominant inflammatory cells, particularly within and adjacent to occasional foci of necrosis or hemorrhage. Rarely, there were small areas of collagen degeneration (“flame figures”) characterized by hypereosinophilic collagen bundles surrounded by free eosinophil granules, intact eosinophils, and fewer neutrophils or macrophages (Fig. 2). Inflammatory infiltrates occurred on a background of marked submucosal or dermal neovascularization (granulation tissue), with capillaries lined by markedly hypertrophic endothelial cells (Fig. 3). Multifocally, within the submucosa or dermis adjacent to the discrete lesions, blood vessels were surrounded by cellular cuffs composed predominantly of eosinophils. A single oral lesion had similar inflammatory cell cuffing surrounding a salivary duct with exocytosis of eosinophils into the duct lumen. In all cases, there was diffuse moderate to marked hyperplasia of the overlying epithelium with formation of numerous branching and anastomosing rete
ridges. Varying degrees of parakeratosis were present. Within the hyperplastic epithelium, there was keratinocyte disorganization, hypogranulosis of the granular cell layer, and hydropic degeneration of keratinocytes with occasional formation of epidermal vesicles. Epithelial changes other than hyperplasia were moderate to marked in four cases and minimal to mild in two cases. In two cases, the original histologic sections were not available for review, and the epithelium could not be evaluated. Toluidine blue staining of two cases revealed low numbers of mast cells distributed widely throughout the lesions. GMS and WS stains were negative for fungi or other microorganisms.

**DISCUSSION**

Several differentials were considered for these eosinophilic inflammatory lesions before choosing to label them as EG. Infection with oomycetes or zygomycete fungi can have eosinophils as a prominent component of the inflammatory response. These mycotic lesions have a greater granulomatous component than was observed in the rhinoceros EG lesions, and fungal elements are usually appreciable. Although it is of interest that two of the animals with EG died of systemic zygomycosis after corticosteroid therapy, the systemic lesions had characteristic granulomatous inflammation without a component of eosinophils, and fungal hyphae were readily identified in histologic sections. Furthermore, the original eosinophilic lesions in those animals resolved in association with corticosteroid therapy, suggesting that the EG lesions and the systemic fungal infections were not related. Eosinophilic and granulomatous lesions have been described from the skin of free-ranging black rhinoceroses infected with the filarid nematode *Stephanofilaria dinniki*. As with the mycotic lesions, filarid infections are associated with more prominent granulomatous inflammation and often have intraleisional microfilariae or adult nematodes that were not observed in any EG lesion. The predominant occurrence of EG lesions within the oral cavity is in contrast to lesions of stephanofilariasis that occur exclusively in the skin and usually on the thorax and abdomen. Similarly, insect bite hypersensitivity, although possibly a differential for cutaneous EG lesions observed in two animals, is not a likely explanation for lesions in the oral or nasal cavity.

Finally, mastocytomas as described in horses can...
have a significant eosinophilic component with areas of collagen degeneration; however, the low numbers of morphologically normal mast cells within the EG lesions was not consistent with this diagnosis.

The mucosal and cutaneous eosinophilic inflammatory lesions in these rhinoceroses clinically and histologically resemble the EG lesions of domestic carnivores and horses. Oral EG, as described in dogs and cats, is characterized by plaques or irregular nodular lesions on the tongue or palate with variable ulceration and may be associated with some degree of patient discomfort. Lesions are usually corticosteroid responsive; however, they may spontaneously resolve and may be recurrent. Unifying histologic features of EG as described in cats, dogs, and horses are eosinophilic inflammation with foci of collagen degeneration that are surrounded by varying degrees of granulomatous inflammation. Lesions in black rhinoceroses are similar to domestic animal EG in that they consist of discrete nodular lesions characterized by prominent dermal and submucosal eosinophilic inflammation with collagen degeneration and have clinical behavior consisting of spontaneous resolution, recurrence, or apparent resolution in response to corticosteroid therapy. Rhinoceros EG differed slightly in anatomic location from those in domestic animals, with oral lesions occurring most often on the labial mucosa immediately behind the prehensile lip. A prominent histologic feature of the EG lesions in black rhinoceroses is the consistent presence of marked intraleisional neovascularization (immature granulation tissue). Although striking, this feature is interpreted as a secondary event because rhinoceros respond to a wide variety of injuries with granulation tissue formation.

Although six of the animals with EG were originally incorporated into the published spectrum of histologic lesions observed with SND, the prominent eosinophilic inflammation in the EG lesions is inconsistent with NME or SND in humans, domestic animals, or even the majority of SND cases in black rhinoceroses. In most black rhinoceroses, SND lesions inflammation was minimal and present only within the dermis or submucosa subjacent to foci of ulceration. This is in contrast to EG, in which the eosinophilic inflammatory component was extensive and present beneath both ulcerated and nonulcerated regions. This difference, com-

**Figure 2.** Oral eosinophilic granuloma, black rhinoceros. A focus of collagen degeneration ("flame figure") is surrounded by multinucleated macrophages and eosinophils. H&E. ×40.
combined with the strong clinical and histopathologic resemblance of the rhinoceros EG lesion to EG in domestic animals, suggests that EG and SND in black rhinoceroses may have a separate pathogenesis.

The prominent epithelial hyperplasia observed in EG lesions from black rhinoceroses is consistent with EG in domestic species in which acanthosis is also a feature.\(^5,23\) However, other epithelial changes observed in some EG cases were suggestive of concurrently manifested SND.\(^12\) These changes, present to a significant degree in four animals, included parakeratosis, hypogranulosis, and marked hydropic degeneration of keratinocytes. The simultaneous occurrence of severe epithelial changes suggestive of SND and the EG lesion could be explained by the frequent occurrence of SND at sites of epithelial tension and trauma.\(^12\) Both SND in dogs and NME in humans have been associated with factors such as glucagonomas, diabetes mellitus, liver disease, or dietary deficiency that result in abnormal glucose metabolism and ultimately, hypoaminoacidemia.\(^2,7,12\) Hypoaminoacidemia is postulated to lead to disruption of epidermal or mucosal homeostasis with resulting cutaneous lesions occurring particularly at locations subjected to stress and injury.\(^2,12\)

The large raised masses observed with the EG lesions would be expected to be easily traumatized and hence more likely to express the morphologic features of SND in a susceptible animal. The simultaneous occurrence of histologic changes suggestive of SND in such a large number of EG lesions is not surprising given the high incidence (up to 50% historically) of SND in the U.S. black rhinoceros population.\(^12\)

The cause of the EG lesions in black rhinoceroses could not be determined. Several potential etiologies have been proposed for EG lesions in domestic species including hypersensitivity reactions,\(^15-18,23\) hereditary factors,\(^15,17,23\) and trauma\(^5,23\); but until recently, none had been conclusively associated with these lesions. Examples of lesions with a demonstrated etiology that previously may have been classified as idiopathic EG include some cases of feline mosquito-bite dermatitis,\(^8\) feline herpesvirus-1-associated facial dermatitis and stomatitis in domestic cats,\(^6\) and equine cutaneous EG associated with reactions to silicone-coated hypodermic needles.\(^20\) These observations are consistent with assertions that histologically similar EG le-
sions in different species may simply be a common morphologic presentation for a variety of inflammatory reactions involving eosinophils.\textsuperscript{3,22} Hereditary factors in the development of EG in dogs and cats have been suggested because of the apparent breed predisposition toward lesion development in Siberian huskies\textsuperscript{15} and Cavalier King Charles Spaniels\textsuperscript{1} as well as by the observation of a high incidence of EG in a closed colony of related specific pathogen–free cats.\textsuperscript{17} Discrete EG lesions as described in this study have not been observed in other species of rhinoceros; as a result, a species-specific predisposition cannot be excluded. The occurrence of EG lesions only in the Eastern black rhinoceros subspecies may simply reflect the higher proportion of this subspecies in the captive population. Rhinoceroses in general, although to a lesser degree than the lesions described in this study, have been observed to respond with eosinophils as a minor component of many cutaneous inflammatory reactions.\textsuperscript{13} EG lesions could then represent an extreme manifestation in some black rhinoceroses of a tendency toward eosinophilic inflammatory responses to a variety of mucosal and cutaneous injuries. The high frequency (six of eight) of oral lesions located behind the prehensile (hook) lip of the black rhinoceros in this study could be significant because this site would be expected to be more frequently traumatized in the process of prehending food. Such regional trauma could lead both to non-specific inflammatory responses that might include eosinophils as well as to localized hypersensitivity reactions as postulated for injection-site EG of horses.\textsuperscript{20} Further investigation of EG in black rhinoceroses might include studies that would address potential initiators of hypersensitivity reactions, additional examination of the genetic background of affected animals as well as exploration of a potential role for as yet unidentified infectious agents, such as viruses.

In summary, EG lesions in black rhinoceroses are clinically and histologically similar to EG observed in domestic animals. Although epithelial lesions characteristic of SND were frequently observed in black rhinoceros EG, it seems likely that these are two concurrently manifest lesions that should be differentiated. Biopsy and histopathology of suspected EG lesions would allow for specific diagnosis and would help exclude other lesions that could resemble EG on gross examination, such as oral neoplasia. Two animals with EG that were treated with corticosteroids developed systemic fungal infections, and this observation is consistent with other occurrences of deep fungal infections in black rhinoceros in which immunosuppression related to corticosteroid therapy has been identified as a possible contributory factor.\textsuperscript{23} These findings suggest that corticosteroid therapy should be used cautiously or avoided in future EG cases with consideration given to other forms of treatment such as cryotherapy.

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LITERATURE CITED


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