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VESICULOBULLOUS SKIN REACTION TEMPORALLY RELATED TO FIROCOXIB TREATMENT IN A WHITE RHINOCEROS (*CERATOTHERIUM SIMUM*)

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Abstract: A 40 yr-old female white rhinoceros (*Ceratotherium simum*) suffered from chronic nail-bed abscesses. Due to worsening of clinical signs, the animal's nonsteroidal anti-inflammatory treatment was switched to firocoxib. Approximately 7 days after this change, the animal developed multifocal vesicles and bullae along the lateral aspects of the thorax and abdomen, the dorsum, and the proximal limbs. Cytology and culture did not identify an infectious etiology. Histologically, the lesions consisted of a severe, subacute vesiculobullous dermatitis with intraepidermal to subepidermal clefting with areas of individual keratinocyte necrosis and minor neutrophilic epidermal infiltrates. These findings are similar to those seen in some drug reactions in people; therefore an adverse drug reaction to the firocoxib was suspected.

Key words: Adverse drug reaction, *Ceratotherium simum*, firocoxib, vesiculobullous dermatitis, white rhinoceros.

BRIEF COMMUNICATION

A 40 yr-old, 1,900-kg white rhinoceros (*Ceratotherium simum*) suffered from chronic, multifocal nail-bed abscesses for 3 yr, beginning in August 2008 and progressing to involve multiple nails on multiple feet. The condition was managed with surgical procedures, nail trimming, hot compresses, foot baths, and topical treatments. In August–September 2008, the rhinoceros received firocoxib (114 mg p.o. s.i.d. for 6 days, followed by 56.8 mg p.o. s.i.d. for 14 days, 8.2 mg/g paste; Equioxx, Merial Limited, Duluth, Georgia 30096, USA) for lameness. Firocoxib is a second-generation coxib nonsteroidal anti-inflammatory drug (NSAID) labeled for the control of pain and inflammation associated with osteoarthritis in horses and dogs. No side effects were observed at this time, and the treatment was discontinued when the lameness improved.

The rhinoceros was treated over the following 2 yr with antibiotics and a variety of other analgesics and anti-inflammatory medications, including tramadol, butorphanol, phenylbutazone and flunixin meglumine, as needed for lameness. Injections of polysulfated glycosaminoglycan (1,000 mg i.m. initially q. 4 days for seven treatments and then once monthly; Adequan, Luitpold Pharmaceuticals, Inc., Shirley, New York 11967, USA) and sodium hyluronidate (80 mg i.v. once monthly; Legend, Bayer Animal Health, Shawnee Mission, Kansas 66201, USA) were initiated several months into treatment and continued for 2 yr.

In December 2010, the rhinoceros's condition had become refractory to treatment and her lameness significantly worsened. Due to rapid worsening of the animal's lameness, analgesics were modified. Treatment with flunixin meglumine was discontinued, and firocoxib (114 mg p.o. s.i.d. for 12 days) was prescribed. The recommended firocoxib dosage for horses is 0.1 mg/kg p.o. s.i.d. for up to 14 days.[1] The dosage selected for this rhinoceros was lower (0.06 mg/kg), due to the convenience of using a single syringe per treatment. This treatment was off-label usage of firocoxib, with no rhinoceros-specific pharmacologic data available.

Seven days after starting treatment with firocoxib, the animal developed multiple vesicles and bullae along the lateral aspects of the thorax and abdomen, the dorsum, and the proximal limbs. Vesicles and bullae ranged in size from 0.5 to 4 cm in diameter and were raised approximately 0.5 to 1 cm. Many of the vesicles contained clear serous fluid, but some contained serosanguineous fluid or pus. Diagnostic evaluation consisted of a complete blood count, serum biochemistry panel, and cytology and bacterial cultures of aspirated fluid. A 5-mm punch biopsy was taken from the

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margin of an intact vesicle and submitted for histopathology. Blood work was unremarkable at this time. Cytology of aspirated vesicular fluid revealed slightly degenerated peripheral blood, with predominantly red blood cells and neutrophils. No bacteria or fungal elements were observed.

On histologic examination of the skin biopsy, the epidermis was almost completely separated from the dermis because of intraepidermal clefting that left only a few multifocal basal cells remaining attached to the dermis. Dilated capillaries within the superficial dermal pegs were occasionally occluded by fibrin thrombi and were accompanied by a mild perivascular infiltrate of lymphocytes, plasma cells, neutrophils, and few eosinophils. Neutrophilic exocytosis and multifocal small vesicopustule formation was present in the separated epidermis. Occasional individually necrotic keratinocytes at different epidermal layers were present along with advanced epidermal cell loss and collapse, the latter of which is common in persistently clefted epidermis. Neither acantholysis nor parakeratosis was a feature. Gram and Giemsa stains were negative for intralesional bacteria. Differentials for the epidermal injury based on histopathology included drug or multidrug reaction, vascular disease, or autoimmune disease. Because the clinical distribution of skin lesions involved the dorsum and because lesions were not more prominent on the face, a high environmental contact area, a contact dermatitis was considered unlikely.

New vesicles and bullae formed over the next several days, and older lesions ruptured, resulting in ulcers. Therapy included topical treatment with dilute chlorhexidine diacetate (Fort Dodge Animal Health, Fort Dodge, Iowa 50501, USA) and silver sulfadiazine cream (1% cream, PAR Pharmaceutical Companies, Inc., Spring Valley, New York 10977, USA). Firocoxib treatment was discontinued 5 days after the development of skin lesions. However, due to a worsening lameness, the animal was euthanized 9 days later. A full necropsy was immediately performed as well as additional diagnostics, including fluid aspiration from intact vesicles and bullae for cytology and culture.

Cytology of the aspirated fluid again lacked cellularity, but the majority of the few cells present were degenerate neutrophils. No bacteria or fungal elements were observed. Bacterial culture of the vesicle fluid grew *Pseudomonas putida* (light growth) and coagulase-negative *Staphylococcus* (moderate growth). No anaerobic bacteria were isolated. These isolates were considered contaminants.

At necropsy, the rhinoceros had 40–60 multifocal to coalescing epidermal vesicles, bullae, and ulcerations that ranged from <1 cm to over 20 cm along the lateral aspects of the thorax and abdomen, the dorsum, and the proximal limbs.

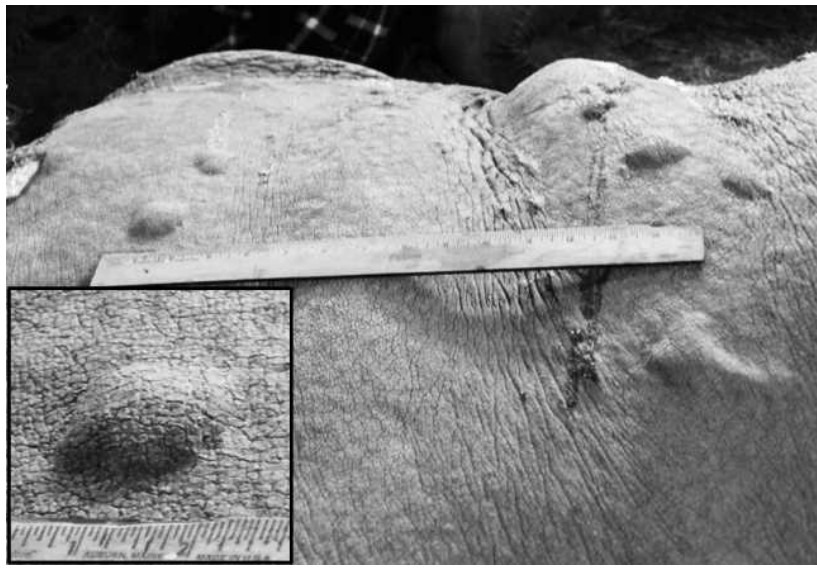

Figure 1. Vesiculobullous dermatitis, skin, white rhinoceros. Multifocal to coalescing raised vesicles and bullae are present on the lateral aspects of the thorax and abdomen, the dorsum, and the proximal limbs. A ruptured lesion drains fluid centrally. Image insert illustrates details of an individual small bulla.

Vesicles and bullae appeared to be limited to the epidermis, were thin-walled, and ruptured easily, containing clear yellow to occasionally purulent fluid (Fig. 1). The epidermis along the back was covered with a thin scaled crust and had linear, vertically oriented fissures, exposable by light traction.

On transverse sections of the second digit of the left front foot, there was an approximately 5-mm-wide draining tract filled with black, friable material, which penetrated the nail at the coronary band and extended to the distal phalangeal bone with separation of the sensitive lamellae. A nearly identical lesion was observed on the third digit of the right hind foot, and similar, less severe tracts that did not extend through the overlying skin were observed in the third and fourth left front digits, the second and fourth right front digits, and the second and third left hind digits. Mild degenerative joint disease was present in the right stifle and tarsus. Additional gross findings included mild, multifocal erosions of the nonglandular stomach. A firm, tan-brown, right adrenal mass ($10 \times 10 \times 25$ cm) contained a central 3–5-cm area of necrosis and calcification and was identified as a complex pheochromocytoma. A firm tan-white mass ($2 \times 3 \times 3$ cm) in the left liver lobe was a hepatocellular adenoma.

Histology of 25 skin lesions was similar to that observed in the biopsies. Intraepidermal microscopic vesicles coalesced and progressed to form bullae and contained clear fluid, or occasionally neutrophils, and were accompanied by only mild individual necrosis of keratinocytes (Fig. 2) in some lesions. With coalescence of intraepidermal vesicles and loss of deep epidermal cells, the epidermis lifted from the dermis to form larger lesions, including bullae. Mixed perivascular

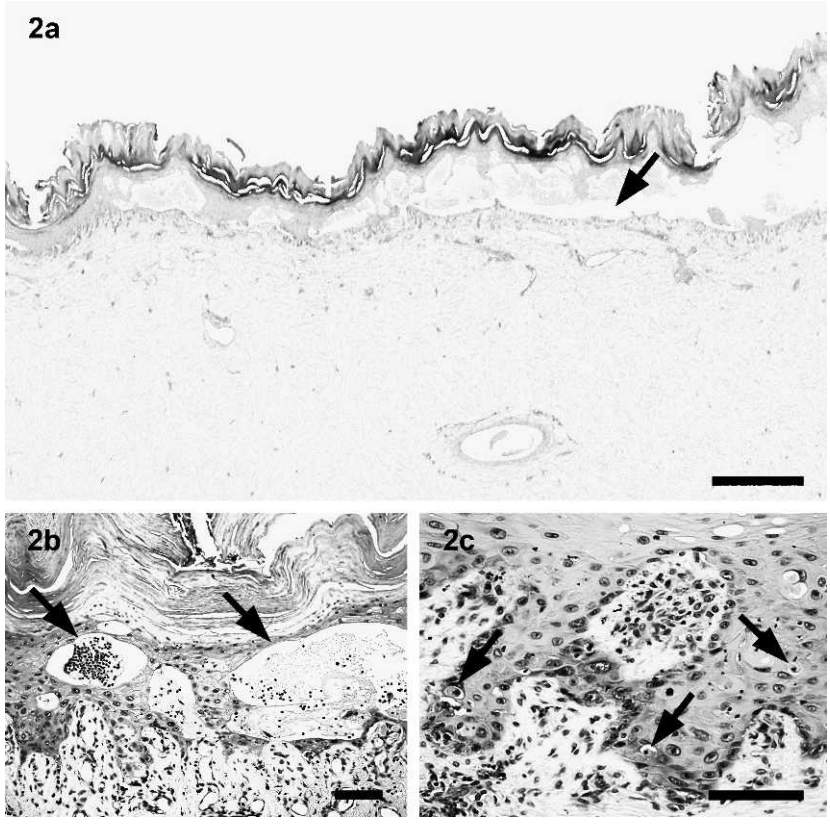

Figure 2. Histopathology of vesiculobullous dermatitis, skin white rhinoceros. **a.** Low-magnification photomicrograph illustrates intraepidermal clefting (arrow) that leads to separation of the epidermis from the dermis, causing vesicles and bullae clinically. (Bar = 1.0 mm.) **b.** Early lesions and bulla margins begin as coalescing small intraepidermal vesicles (arrows) that contain clear fluid and/or neutrophils, which extend to appear subepidermally with loss of keratinocytes. (Bar = 100 μm.) **c.** Mild multifocal single-cell necrosis of keratinocytes (arrows) at different epidermal levels was evident in only some lesions. (Bar = 100 μm.) Hematoxylin and eosin.

inflammation was a minor feature that was nearly absent in early lesions and contained neutrophils, lymphocytes, and plasma cells. Lymphocytic exocytosis was minimal. Neither vascular lesions nor parakeratosis were features. Bacteria were only present in neutrophilic crusts on secondary ulcers.

Adverse reactions occurred in horses treated with firocoxib during animal safety studies, including erosions and ulcers of the mucosa and skin of the mouth and face.[1] In dogs, vomiting has been reported as an adverse event secondary to firocoxib treatment,[3] but no adverse effects were noted on hematologic or serum biochemical values after 29 days of treatment.[7] NSAIDS have also been reported to cause bullous-type adverse skin reactions in people.[5] While firocoxib treatment is suspected, another cause for skin lesions in this white rhinoceros is difficult to completely exclude. The patient received other drugs, but these treatments were not temporally related to skin lesion development. Although considered unlikely, the patient could have developed a paraneoplastic dermatopathy secondary to either the adrenal complex pheochromocytoma or hepatocellular adenoma identified at necropsy.

Drug reactions encompass all adverse events related to drug administration, regardless of etiology, whereas drug hypersensitivity is defined as an immune-mediated response to a drug agent in a sensitized patient.[6] A diagnosis of drug hypersensitivity is based on clinical signs, the temporal sequence of drug administration, and ruling out other causes because confirmatory drug-specific testing is often difficult.[6] In this rhinoceros, it is possible that the initial firocoxib treatment, 28 mo prior to this episode, sensitized the animal to the drug. Clinical signs were first observed at 7 days, which is consistent with the timing of a drug hypersensitivity reaction in people.[6]

A vesicular and ulcerative dermatopathy resembling superficial necrolytic dermatitis has been described in captive black rhinoceros (*Diceros bicornis*).[4] However, the dermatopathy observed in this white rhinoceros differs from the disease described in black rhino, where the histopathologic findings include prominent acanthosis, hydropic degeneration of keratinocytes in the stratum spinosum, spongiosis, intraepithelial vesicles, and parakeratosis without dermal inflammation.[4] In addition, vesicular skin disease has been described in a tapir,[2] also in the order Perissodactyla. This female lowland tapir (*Tapirus terrestris*) had multifocal subepidermal vesicles with histopathology of severe spongiosis, superficial to transepidermal necrosis, severe perivascular edema surrounding dermal vessels, and regionally severe hemorrhage in the superficial dermis.[2]

This report describes a vesiculobullous skin reaction temporally related to firocoxib treatment in a white rhinoceros. Although a causal relationship was not proven in this case, clinicians should be aware of the possibility of an adverse skin reaction when administering firocoxib to patients.

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