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PATHOLOGY

Nasal mucosal mineralization, ulceration and epistaxis in a dog with uremia caused by chronic renal failure

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ABSTRACT: *Soft tissue mineralization and epithelial ulceration are common findings in dogs with uremia, being commonly reported in the gastrointestinal tract, lungs and pleura. This report described a case of nasal mucosal mineralization and ulceration contributing to recurrent epistaxis in a dog with chronic renal failure and uremia. A dog with recurrent epistaxis accompanied by elevated urea and creatinine was hospitalized. Platelet count and coagulation tests were within normal limits. Chronic renal failure was diagnosed, and the dog was euthanized. On necropsy, the kidneys were small, with an irregular capsular surface. The nasal conchae were slightly reddish. Histopathology revealed chronic glomerulonephritis, with gastric mineralization and bilateral parathyroid hyperplasia. Vascular and basal lamina mineralization, epithelial ulceration and hemorrhage were seen in the nasal conchae. The observed findings indicated that nasal mineralization and ulceration were caused by uremia. The severity of histopathological findings suggested that nasal mineralization/ulceration may have caused or at least contributed to epistaxis in this dog. We hope to stimulate further investigations into possible association between uremia, nasal mucosa mineralization/ulceration and epistaxis in dogs.*
Key words: *renal failure, nasal bleeding, secondary hyperparathyroidism, extrarenal uremic lesions, hemorrhage.*

Mineralização, ulceração e epistaxe em um cão com uremia causada por insuficiência renal crônica

RESUMO: *Mineralização dos tecidos moles e ulceração epitelial são achados comuns em cães com uremia, sendo geralmente observados no trato gastrointestinal, pulmões e pleura. O objetivo desse relato é reportar um caso de mineralização e ulceração da mucosa nasal contribuindo para epistaxe recorrente em um cão com insuficiência renal crônica e uremia. Um cão com epistaxe recorrente e aumento da ureia e creatinina foi hospitalizado. A contagem plaquetária e os testes de coagulação não tinham alterações. Foi diagnosticado insuficiência renal crônica, e o cão foi submetido a eutanásia. Na necropsia, o cão tinha os rins diminuídos, com superfície irregular. As conchas nasais estavam levemente avermelhadas. Histologicamente, foi diagnosticada uma glomerulonefrite crônica com mineralização gástrica e hiperplasia das paratireoides. As conchas nasais tinham mineralização da parede de vasos e membrana basal, úlceras e hemorragia. Os achados histopatológicos indicam que a mineralização e ulceração nasal foram causadas pela uremia. A severidade das lesões histológicas sugere que a mineralização/ulceração nasal pode ter causado, ou pelo menos contribuído, para a epistaxe deste cão. Espera-se, com esse relato, estimular futuros estudos que investiguem uma possível associação entre uremia, mineralização/ulceração nasal e epistaxe em cães.*
Palavras-chave: *insuficiênia renal, sangramento nasal, hyperparatireoidismo secundário, lesões extrarrenais de uremia, hemorragia.*

Soft tissue mineralization and epithelial ulceration are common lesions in dogs with uremia, being commonly observed in the gastrointestinal tract, lungs and pleura (CIANCIOLO & MOHR, 2016). These lesions have not been reported in the nasal mucosa of uremic dogs. Epistaxis is defined as hemorrhage from the nasal cavity, being possibly associated with systemic or intranasal disease BISSET et al., 2007; MYLONAKIS et al., 2008). Despite of being mentioned as a cause of epistaxis, renal failure seems to be rarely associated with this clinical sign in dogs, and generally leads to epistaxis by indirect mechanisms, such as systemic hypertension (BISSET et al., 2007; MYLONAKIS et al., 2008). This study described nasal mucosal mineralization and ulceration contributing to recurrent epistaxis in a dog with chronic renal failure and uremia

A 14-year-old male Border Collie was presented to the Hospital Veterinário Universitário (HVU) of the Universidade Federal de Santa Maria (UFSM) with a week history of apathy, inappetence and epistaxis. The dog was in good body condition and showed uremic halitosis. The nasal cavity did not have any alterations on endoscopic examination.

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During the next seven days, recurrent episodes of bilateral epistaxis were noted. There was increased urea (500 mg/dL, reference value [RV]: 9-26mg/dL), creatinine (7.9 mg/dL, RV: 0.6-1.4mg/dL) and serum phosphate (13.4 mg/dL, RV: 2.5-6 mg/dL). Urine density was 1008 (RV: 1015-1045) and the systemic arterial blood pressure was increased (220 mmHg, RV: 130-150 mmHg). The dog had a non-regenerative anemia (hematocrit 27.6%, RV: 37-55%; 3.97x106/uL red blood cells, RV: 5.7-8.5 x106/uL; 69.0 fL VCM, RV: 64-76 fL; 34,5% CHCM, RV: 33-36%). The platelet count was within normal limits (3(381,000/uL, rV: 200,000-500,000/uL), and the leukogram was unremarkable. Prothrombin (6.72 seconds, RV: <22 seconds) and activated partial thromboplastin (6.72 seconds, RF: <20 seconds) times were normal. On abdominal ultrasound, the kidneys were decreased in size. An antibody snap test for leishmaniosis (Alere®) was negative. A lymph node cytology failed to detect infectious organisms consistent with Leishmania spp. A clinical suspicion of chronic renal failure was established. The animal was submitted to euthanasia and necropsy was performed.

The mucosal membranes were moderately pale. The kidneys were small, with an irregular capsular surface, and on cut surface, the cortex was moderately decreased in width and contained several 0.2 to 0.3 cm in diameter liquid-filled cysts. The parathyroids were increased (0.5 x 0.4 x 0.3 cm in diameter each) (Figure 1A). The nasal mucosa and conchae were discretely reddish (Figure 1B). Samples from kidneys, liver, spleen, parathyroids, lungs, stomach, heart, bone marrow, nasal conchae and eyes were fixed in 10% buffered formalin, routinely processed for histopathology and stained with Hematoxylin and Eosin. Histopathologic exam revealed a chronic severe membranous glomerulonephritis, characterized by global hyaline thickening of the glomerular capillary basement membranes and interstitial fibrosis. The parathyroids were diffusely and severely enlarged by chief cell hyperplasia. The gastric mucosa had multifocal mineralization, and moderate fibrinoid necrosis was observed in some small arteries of the gastric submucosa. The nasal conchae had multifocal areas of vascular wall and basal lamina mineralization (Figure 1C). Multiple small vessels in the lamina propria also contained fibrin thrombi. Additionally, the lamina propria was edematous, with multifocal hemorrhages (Figure 1D). Multifocal areas of loss of the superficial ciliated epithelium with destruction of the basement membrane (ulceration) were frequent. These areas were often infiltrated by degenerate and viable neutrophils and covered by granular, basophilic material that stained brown-black with Von Kossa special stain (mineralization) (Figure 1E). The trabecular bone from the nasal conchae displayed a moderate increase in lining osteoclasts and was partially replaced by proliferating fibroblasts (fibrous osteodystrophy) (Figure 1F). An erythroid hypoplasia was diagnosed in the bone marrow.

Nasal mineralization and ulceration are rarely reported in animals. In this case, the possibility of these nasal changes being associated with epistaxis makes them even more unusual (CIANCIOLO & MOHR, 2016). The dog from this report had persistent hypertension during hospitalization, which was thought to be the sole cause for epistaxis. However, the histologic features and severity of nasal lesions strongly suggest that these changes may have caused or at least contributed to nasal bleeding in this case. Although, nasal injuries, mainly primary neoplasia, are the most common causes for epistaxis in dogs (BISSET et al., 2007; MYLONAKIS et al., 2008), systemic conditions can also be incriminated as a cause for nasal bleeding (HAWKINS, 2015; BISSET et al., 2007). Uremia can cause vascular injury; however, it has not been reported as a predisposing factor for nasal bleeding (CIANCIOLO & MOHR, 2016). Leishmaniasis was an important differential diagnosis in this case, since this dog lived in an endemic region for this infectious disease (JÜTTNER et al., 2001), however, both snap test and lymph node cytology were negative.

Epistaxis is not a common clinical sign of renal failure in domestic animals, and when reported, it is generally attributed to indirect mechanisms, such as hypertension (BISSET et al., 2007; MYLONAKIS et al., 2008; CIANCIOLO & MOHR, 2016), and less commonly, increased capillary fragility, disseminated intravascular coagulation and other coagulation abnormalities (CIANCIOLO & MOHR, 2016). In humans with renal disease, epistaxis is associated with hypertension or part of a uremic bleeding syndrome (HEDGES, et al. 2007). Although, the pathogenesis of epistaxis in this latter condition is still poorly understood, it is probably multifactorial. Studies regarding nasal bleeding in humans with renal failure make no reference to uremia-associated nasal mineralization as a cause for this clinical sign (HEDGES et al., 2007).

Uremia is a common sequel of chronic renal failure, characterized by an increase in circulating uremic toxins, which is toxic to blood vessel endothelial cells. Therefore, small arterioles develop vascular wall fibrinoid necrosis, which leads

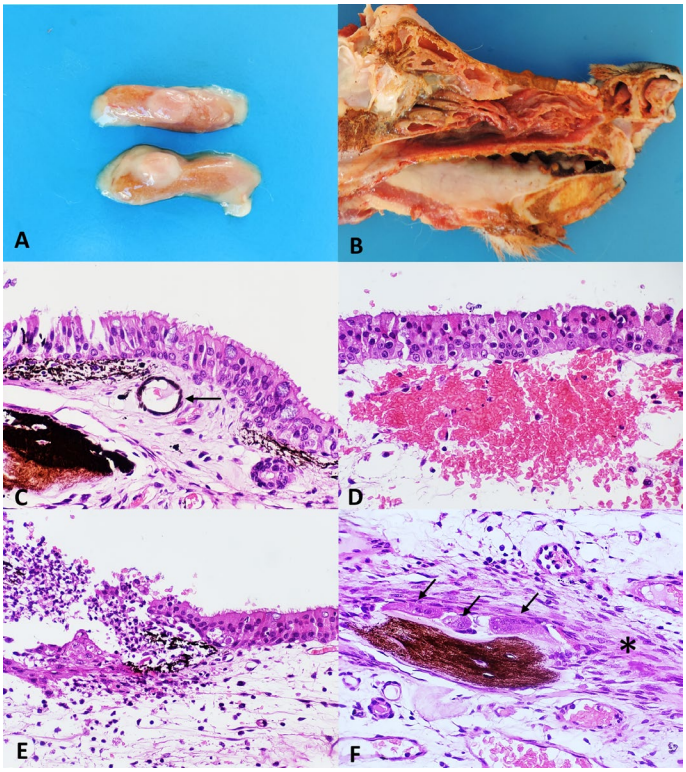

Figure 1 - Nasal conchae mineralization, ulceration and acute hemorrhage in a dog with chronic renal failure and uremia. (A) The parathyroids are diffusely enlarged. (B) The nasal conchae are discretely reddish. (C) Vascular wall (arrow) and basal lamina mineralization within a nasal concha (Von Kossa special stain [VK] counterstained with Hematoxylin and Eosin [HE], Obj 40X). (D) Severe hemorrhage within the lamina propria mucosae of a nasal concha (HE, Obj 40X). (E) Focal area of ulceration with exposure of a mineralized lamina propria mucosae (stained in black-brown), infiltration of neutrophils and extravasation of erythrocytes within the nasal conchae ciliated epithelium (VK counterstained with HE, Obj 20X). (F) A bone trabecula from a nasal concha is surrounded by multiple osteoclasts (arrow) and partially replaced by fibroblasts and collagen (asterisk) (VK counterstained with HE, Obj 40X).

to thrombosis, ischemia, and possible subsequent ulcerations of the affected organs. Vascular necrosis is often accompanied by vascular wall mineralization (CIANCIOLO & MOHR, 2016). The sequence of vascular fibrinoid necrosis, thrombosis and ischemia is often responsible for bleeding through the affected mucosa, observed, for instance, in the stomach of uremic dogs. For this reason, melaena is frequent in these patients (CIANCIOLO & MOHR, 2016). In the present case, the presence of vascular thrombosis and mineralization within nasal conchae as well as its association with severe nasal ulceration, strengthen the suspicion that the nasal lesions were the cause of the observed epistaxis. We cannot ignore the fact; however, that this dog had systemic hypertension, which is an important cause of epistaxis in this species, and in our opinion, has possibly contributed to nasal bleeding in this patient. Nevertheless, considering that hypertension does not cause nasal mineralization and ulceration, we strongly believe that it was not solely responsible for epistaxis in this dog. Rough nasal conchae examination is not a routine procedure during necropsy, which could lead to an underdiagnosis of this lesion in uremic dogs without

nasal bleeding. We hope this report will stimulate further research on a possible association between uremia-induced nasal mineralization/ulceration and epistaxis in dogs with chronic renal failure.

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AUTHORS' CONTRIBUTIONS

The authors contributed equally to the manuscript.

DECLARATION OF CONFLICT OF INTEREST

We have no conflict of interest to declare.

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