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Fibrous osteodystrophy due to secondary renal hyperparathyroidism in a senile dog

[*Osteodistrofia fibrosa decorrente de hiperparatireodismo secundário renal em cão senil*]

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ABSTRACT

Renal hyperparathyroidism stands out among the complications of kidney disease in dogs due to phosphorus retention with a predisposition to hypocalcemia, parathyroid hormone stimulation with mobilization of calcium from the bones, characterizing fibrous osteodystrophy, unusual in the elderly. The objective was to report it in 12-year-old Labrador with polyuria, polydipsia, and emesis for five months due to maxillary and mandibular volume increase, followed by loosely fixed teeth, and facial deformity. Blood tests showed anemia, thrombocytosis, azotemia, hypoalbuminemia and hyperphosphatemia and urinalysis showed low density, glycosuria, proteinuria, and moderate caudate and transitional epithelial cells. Oral x-rays showed loss of dental bone support and decreased bone radiopacity. Chest radiographs showed decreased density in the ribs and costochondral junction; on the other hand, organs of the cardiorespiratory system showed no changes. The electrocardiogram and echocardiogram did not show impairment. Abdominal ultrasound revealed kidneys with asymmetry, increased echogenicity of the cortical and poorly preserved cortico-medullary definition. Oral histopathology showed intense fibroplasia associated with bone reabsorption. Support therapy was instituted, but the patient died ten days after consultation. Thus, although uncommon in the elderly, fibrous osteodystrophy should be investigated in dogs with advanced-stage chronic kidney disease and, even with conservative therapies, the prognosis is unfavorable.

Keywords: chronic kidney disease, hyperphosphatemia, hypocalcemia, renal fibrous osteodystrophy, rubber jaw

RESUMO

O hiperparatireoidismo renal destaca-se entre as complicações da doença renal em cães, pela retenção de fósforo com predisposição à hipocalcemia, estimulação de paratormônio com mobilização do cálcio dos ossos, caracterizando a osteodistrofia fibrosa, incomum em idosos. O objetivo foi relatá-la em Labrador de 12 anos com poliúria, polidipsia e vômitos há cinco meses, além de aumento de volume maxilar e mandibular seguido de dentes frouxamente fixados e deformidade facial. Os exames sanguíneos denotaram anemia, trombocitose, azotemia, hipoalbuminemia, hiperfosfatemia, urinálise, baixa densidade, glicosúria, proteinúria e moderadas células caudadas e epiteliais de transição. Pelos raios X orais, houve perda da sustentação óssea dentária e diminuição da radiopacidade óssea. As radiografias de tórax demonstraram diminuição da densidade óssea na região dos arcos costais e junção costocondral; em contrapartida, órgãos do sistema cardiorrespiratório se mostraram sem alterações aparentes. O eletrocardiograma e o ecocardiograma não incidiram comprometimento. O ultrassom abdominal revelou rins com assimetria, aumento da ecogenicidade cortical e definição corticomedular pouco preservada, e a histopatologia oral apontou intensa fibroplasia associada à reabsorção óssea. Foi instituída terapia suporte, mas o paciente veio a óbito 10 dias após a consulta. Assim, mesmo que incomum em idosos, a osteodistrofia fibrosa deve ser investigada em cães com doença renal crônica em estágio avançado, e, mesmo com as terapias conservadoras, o prognóstico é desfavorável.

Palavras-chave: doença renal crônica, hiperfosfatemia, hipocalcemia, mandíbula de borracha, osteodistrofia fibrosa renal

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INTRODUCTION

The kidneys play a key role in maintaining the organic system, and eventual imbalances interfere with homeostasis, directly affecting the quality of life and survival of those affected. In this context, chronic kidney disease (CKD) is the most diagnosed nephropathy in senile dogs (Castro *et al*., 2007; Waller *et al.*, 2019), characterized by the progressive and irreversible loss of structural and/or functional capacity of one or both kidneys, in a course of more than three months (Bartges, 2012; Dunaevich *et al*., 2020).

In addition to the functions of glomerular filtration, with excretion of compounds through the urine and reabsorption through the proximal tubules, the kidneys have an endocrine function, act in the maintenance of blood pressure through the renin angiotensin aldosterone system and are involved in the regulation of the acid-base state (Alves *et al.*, 2014; Sargent *et al.*, 2021). Therefore, the decrease and/or loss of renal function culminates in the interruption of these physiological processes and compounds that should be excreted are retained, such as phosphorus and creatinine, while water and proteins are eliminated (Bartges, 2012; Moraes *et al*., 2020).

Clinical manifestations include deficient body condition, opaque fur, lethargy, hyporexia and/or anorexia, weight loss, polyuria, compensatory polydipsia, emesis, dehydration, pale mucous membranes, ulcerative stomatitis, halitosis, arterial hypertension, and facial deformity (Castro *et al.*, 2007; Bartges, 2012; Alves *et al.*, 2014). In the hematological evaluation, it is possible to detect azotemia, non-regenerative anemia, hypoalbuminemia, hyperphosphatemia, hyperkalemia or hypokalemia, and metabolic acidosis. On urinalysis, decreased ability to concentrate urine, cylindruria, and proteinuria, the latter associated with a worse prognosis (Polzin, 2011; Moraes *et al*., 2020). Due to the irreversible and progressive character of CKD, the treatment is symptomatic and lifelong (Bartges, 2012; Dunaevich *et al*., 2020).

Among the complications of CKD at an advanced stage, secondary renal hyperparathyroidism stands out (Polzin, 2011), a complex and multifactorial syndrome, resulting from plasma phosphorus retention and vitamin D deficit (Castro *et al.*, 2007; Alves *et al.*, 2014). Hyperphosphatemia predisposes to hypocalcemia due to the formation of phosphorus-calcium complex, which potentiates the synthesis of parathyroid hormone (PTH) by the parathyroid glands (Freitas *et al*., 2017).

In this sense, although unusual in dogs (Alves *et al.*, 2014) and cats seniles (Nagode *et al.*, 1996), the exacerbated increase in PTH can mobilize calcium from the bones, causing fibrous osteodystrophy, also known as renal osteodystrophy (Alves *et al.*, 2014; Waller *et al.*, 2019), characterized by an osteopenic disorder with intense proliferation of fibrous connective tissue. Also, in CKD there is a decrease in calcitriol levels, further contributing to hypocalcemia, increasing the release of PTH (Alves *et al.*, 2014).

Fibrous osteodystrophy can also be caused by nutritional disorders such as a diet rich in phosphorus and low in calcium (Polzin, 2011; Freitas *et al.*, 2017; Silva *et al.*, 2020). This condition mainly affects the bones of the face, in particular the maxillary and mandibular region ("rubber jaw") of growing animals (Rusenov, 2010; Polzin, 2011; Alves *et al.*, 2014; Waller *et al.*, 2019) due to incomplete skeletal maturation in this age group (Rusenov, 2010; Polzin, 2011), causing facial deformity (Freitas *et al.*, 2017). Oral bone resorption probably occurs due to excess PTH combined with increased concentration of fibroblast growth factor 23 (FGF 23), which increases renal phosphorus excretion and suppresses the synthesis of 1,25-calcitriol by decreasing the activity of 1α-hydroxylase enzyme in the kidneys (Polzin, 2011; Waller *et al.*, 2019). According to Nagode *et al.* (1996), so far, there are no scientific explanations for the mandibular and maxillary bones being predisposed to diffuse density loss.

Given the unusual occurrence of fibrous osteodystrophy in adults dogs, this report aimed to describe this condition in an elderly canine, due to secondary renal hyperparathyroidism, emphasizing its clinical, hematological, urinary, radiographic, ultrasonographic, cardiological and oral histopathological changes.

CASE REPORT

A 12-year-old canine patient, Labrador, male, not neutered was treated at the Veterinary Hospital of the University of Franca, presenting hyporexia, halitosis, polyuria, polydipsia, and sporadic emesis for five months. Physical examination revealed cachexia, bilateral maxillary, and mandibular swelling, followed by loosely fixed dental elements and facial deformity (Fig. 1), in addition to reactive mandibular lymph nodes and pale mucous membranes. The other parameters were within the normal range for the species.

On the same day of the consultation, complementary hematological and urinary tests, oral and thoracic x-rays, electro and echocardiogram and abdominal ultrasound were performed.

The hematological examination detected normocytic normochromic anemia (hematocrit 26.3%, red cells 3,900,000µL and hemoglobin 8.8g/dL), thrombocytosis (526,000), marked azotemia (creatinine 7.3mg/dL and urea 256mg/dL), hypoalbuminemia (2.2g/dL) and hyperphosphatemia (14.6 mg/dL).

Urinalysis showed low urinary density (1.010), glycosuria (+), proteinuria (++) and moderate caudate and transitional epithelial cells. The urinary protein/creatinine ratio was 10.1.

Figure 1. Photographic image of an elderly Labrador with bilateral maxillary enlargement with consequent facial deformity.

The maxillary and mandibular radiographic examination, in the right latero-lateral (Fig. 2A) and ventro-dorsal (Fig. 2B) views, indicated loss of bone support of the dental elements and generalized decrease in bone radiopacity ("rubber jaw"), being compatible with fibrous osteodystrophy.

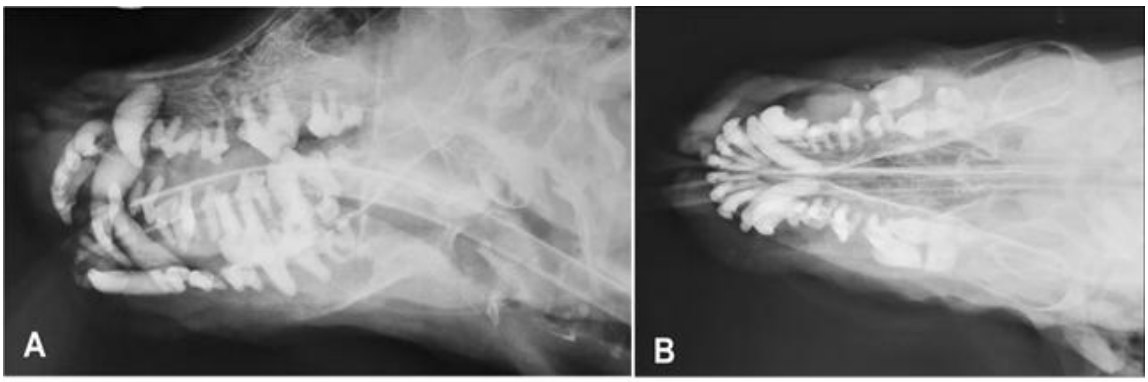

Figure 2. Radiographic images of the mandible and maxilla of an adult dog, in the right latero-lateral (A) and ventro-dorsal (B) views, showing dental elements loosely fixed in the respective alveoli and generalized decrease in bone radiopacity, suggestive of fibrous osteodystrophy (“rubber jaw”).

Chest radiographs also showed a decreased bone density in the region of the ribs and costochondral junction; on the other hand, organs of the cardiorespiratory system apparently showed no changes, including heart size, lung pattern and tracheal position. The electrocardiogram and echocardiogram exams did not demonstrate impairments.

Ultrasonographic evaluation detected kidneys in the usual topography, asymmetric, with increased echogenicity of the cortical region and poorly preserved corticomedullary definition (Fig. 3). The other organs were within the normal range for the species and no reactive lymph nodes were detected.

Given the uncommon occurrence of fibrous osteodystrophy in senile dogs and the mandibular and maxillary radiographic findings found in the reported patient, it was anesthetized (two days after the consultation) to collect bone fragments, aiming for an histopathological examination to rule out the possibility of neoplasia with resorption character, isolated or in association with fibrous osteodystrophy. Furthermore, this complementary examination aimed to elucidate the characteristics of fibrous osteodystrophy in elderly animals, compared to young ones, given the scarcity of these data in the scientific literature. Histopathological examinations showed intense fibroplasia, containing discrete bone trabeculae with marked osteoclastic activity and multifocal areas of calcification, suggestive of fibroplasia associated with bone reabsorption (Fig. 4).

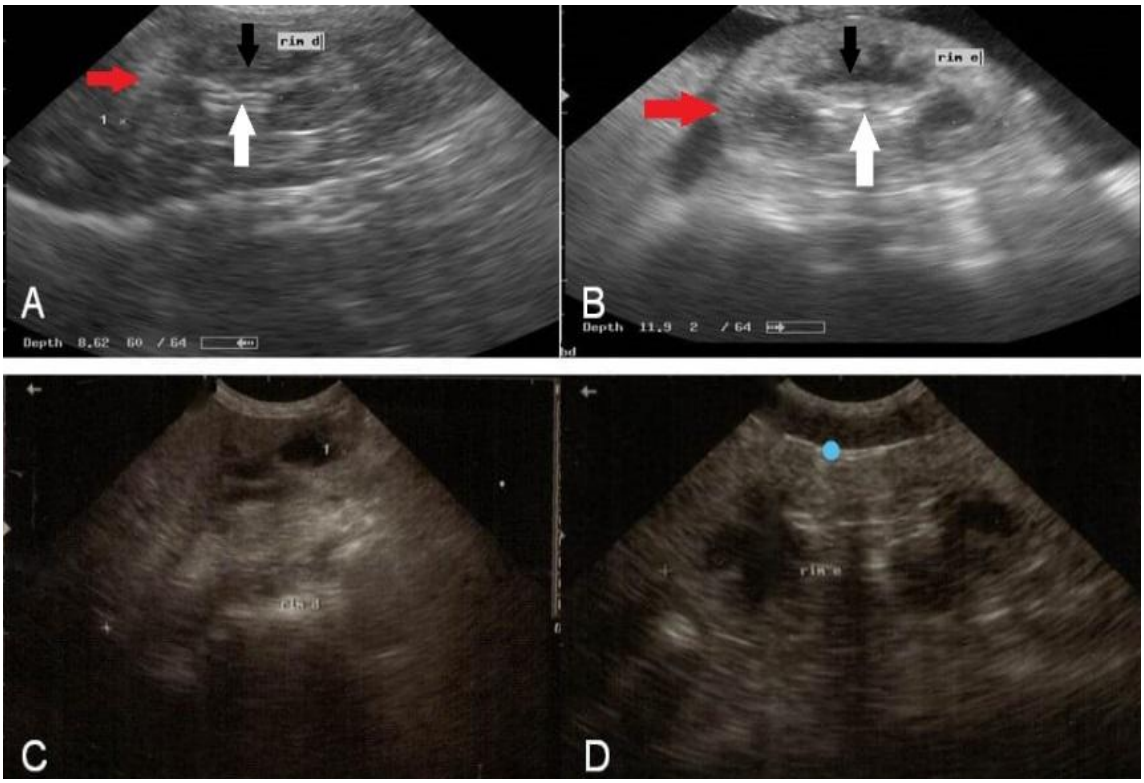

Figure 3. Ultrasonographic images of the right and left kidneys of a healthy dog (A and B), demonstrating regular contours, echogenicity, preserved architecture and texture, in addition to cortical (red arrows) medullary (black arrows) definition and absence of calcification, lithiasis and hydronephrosis. Renal hilum (white arrows) preserved. On the other hand, ultrasound images of the right and left kidneys of a dog with chronic kidney disease (C and D), showing irregular contours, generalized increase in echogenicity, loss of corticomedullary architecture and definition.

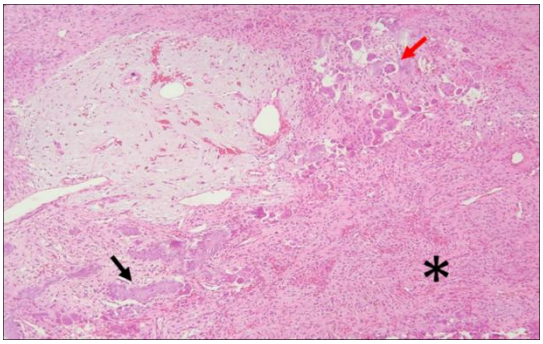

Figure 4. Oral bone photomicrograph of a dog, showing intense fibroplasia (asterisk), containing discrete bone trabeculae between them (black arrow) with marked osteoclastic activity (red arrow). H.E. obj.10x.

On the same day, as the animal was fasting and, because of glycosuria, blood glucose was performed, which showed no change, ruling out diabetes as a comorbidity.

Based on the historic, anamnesis, physical examination, laboratory, imaging, cardiological and histopathological tests, the patient was diagnosed with fibrous osteodystrophy secondary to chronic kidney disease, stage 4 according to International Renal Interest Society (IRIS, 2019).

Despite the long period that elapsed between the appearance of clinical signs and the consultation (five months) and the unfavorable prognosis, conservative treatment was instituted with intravenous fluid therapy (Ringer Lactate 100mL/kg, per day), vitamin and iron supplementation (Hemolitan Pet®, 30mL, orally, every 12 hours), appetite stimulant (cyproheptadine hydrochloride, 0.1ml/kg, orally, every eight hours), gastric protector (Omeprazole 1mg/kg, orally, every 12 hours), phosphorus binders (aluminum hydroxide 25mg/kg, orally, every 12 hours), erythropoietin (100IU/kg, subcutaneous injection, three times a week) and a diet with reduced levels of phosphorus and protein. Even with the institution of supportive treatment, the animal showed no improvement and died ten days after the consultation.

DISCUSSION

Despite the uncommon occurrence of fibrous osteodystrophy in adult dogs, Alves *et al.* (2014) also reported two cases in senile males, one Labrador and one mixed breed of 11 and 10 years, respectively and Freitas *et al.* (2017) in a nine-year-old mixed breed female.

Regarding the systemic clinical signs presented by the reported patient, they corroborated those described in the eight-month-old young dog by Castro *et al.* (2007), as well as in the two elderly dogs specified by Alves *et al.* (2014) and Freitas *et al.* (2017), including the osteopenic disorder, characterized by osteoclastic reabsorption of bone trabeculae associated with proliferation of fibrous connective tissue and deficient mineralization of osteoids (Polzin *et al.*, 2011; Waller *et al.*, 2019). In the patient of the present report, the severity of fibrous osteodystrophy could be observed by mandibular and maxillary radiographic images, since the bone demineralization is only detected radiographically when there is a loss of 30% to 50% of bone mass (Lazaretti *et al.*, 2006). Although rarefaction makes the bones more mobile and sensitive, it did not cause pathological fractures in that patient (Rusenov, 2010; Alves *et al.*, 2014). Due to the scarcity of cases addressing the oral bone histopathological aspects of adult dogs with fibrous osteodystrophy, the discussion of this aspect has become restricted. Similarly, by staining with hematoxylin-eosin, Rusenov *et al.* (2009) described a reduction in the amount of mandibular bone tissue associated with connective tissue deposition in an 11-month-old German Shepherd, as well as Hines *et al.* (2021) in a 6-year-old female dromedary camel, however with secondary nutritional hyperparathyroidism.

Usually in CKD, polyuria with consequent polydipsia are the first symptoms evidenced in dogs (Bartges, 2012); however, the patient in question presented persistent polyuria and polydipsia, associated with gastrointestinal disorders, anemia, hypoalbuminemia, intense azotemia, low urinary density and severe proteinuria, suggesting severe impairment of renal function (Castro *et al.*, 2007; Waller *et al.*, 2019), that according to Alves *et al.* (2014), is on account of the hydroelectrolyte imbalance and increased serum concentrations of residues, due to a reduction in the glomerular filtration rate, when at least 75% of nephrons are lost. As a result of severe renal impairment, the aforementioned patient had renal glycosuria as the kidneys do not reabsorb the glucose filtered

by the glomeruli and eliminated it in the urine (Fishman *et al.*, 2019; Zeugswetter and Schwendenwein, 2020). In this theme, blood glucose test was performed with the patient in prolonged fasting to rule out the presence of concomitant mellitus diabetes.

The anemia of the described patient can be explained by the insufficiency of the renal secretion of erythropoietin, which has the function of stimulating the production of red blood cells by the bone marrow (Waller *et al.*, 2019), justifying the exogenous administration of this hormone.

According to Roe and Cassidy (2000), the decrease in serum albumin is directly related to persistent and long-term proteinuria, being an important marker of renal function; and, despite the presence of proteinuria and hypoalbuminemia in the elderly dog reported, it did not show edema and ascites that could characterize the development of nephrotic syndrome.

The sonographic findings of the dog in question were similar to those of the elderly patient described by Freitas *et al.* (2017).

The cardiological exams of the patient reported did not show significant changes, even though chronic kidney disease represents a risk factor for the development of congestive heart conditions, including heart failure and its complications, which can drastically impair the quality of life and survival of those affected (Romero-González *et al.*, 2020).

Even with the institution of supportive treatment, most of those affected by CKD at an advanced stage do not show improvement in their clinical condition and die or are euthanized due to the worsening of the uremic condition (Alves *et al.*, 2014), consistent with the evolution of the reported patient.

CONCLUSION

Although uncommon in elderly dogs, fibrous osteodystrophy should be investigated in animals with advanced-stage chronic kidney disease because it is severe and causes systemic impairment, including alteration of bone matrix rigidity by connective tissue. Nevertheless, clinical, hematological, urinary, radiographic, ultrasonographic and histopathological findings of senile dogs are similar to young dogs and, regardless of age, the prognosis is unfavorable despite the institution of supportive therapy.

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