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CASE REPORT

OSTEODYSTROPHIA FIBROSA SECONDARY TO A CHRONIC RENAL FAILURE IN A DOG: A CASE REPORT

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Abstract

A five year male Rottweiler was presented to the Small animal clinic of the Veterinary Teaching Hospital, University of Ibadan, being a referral from Lagos. Bilateral swelling and deformity of the skull bones were observed. Palpation revealed swollen gums and weak mobile teeth weak. Urination was frequent and the urine very clear. Haematology and blood chemistry revealed non-regenerative anaemia, mild leucopenia, hypocalcaemia, hyper-phosphataemia, high serum blood urea and creatinine, and hyper-bilirubinaemia. Treatment was instituted with dextrose saline to rehydrate the animal and correct electrolyte and metabolic disorders. The dog however died despite intervention. At post mortem, the carcass was found to be jaundiced, the premolars were mal-positioned. Calcification was visible on the lower jaw. Kidneys were small, firm, with many white specks on the cortical surface. A diagnosis of Uremic renal failure with Osteodystrophia fibrosa (renal rickets) was made. The possible causes and clinical implications of the condition were discussed.

Introduction

Specific factors implicated in fibrous osteodystrophy include the rare primary hyper-parathyroidism, usually occurring in aged dogs caused by a functional parathyroid gland adenoma (Thompson *et. al.*, 1984; Capen and Martin (1977), and the more common secondary renal hyperparathyroidism which results from renal disease or nutritional imbalance (calcium deficiency, excessive potassium or Vitamin D deficiency (Palmer, 1968; Thompson and Robinson, 1989; Bandarra *et. al.* 2011). Specifically, all-meat diets have been implicated in nutritional secondary hyper-parathyroidism causing fibrous osteodystrophy (Thompson *et. al.* 1984).

Renal osteodystrophy has been described as a skeletal complication of end-stage renal disease and as a "multifactorial disorder of bone remodelling" (Keith, 1998). The link between chronic renal failure and secondary renal hyperthyroidism, resulting in renal osteodystrophy has been severally discussed in literature (Rusenov *et al.*, 2009, Rusenov, 2010, Vadhan and Hutchinson, 2009, Fraser, 2009).

Secondary renal hyper-parathyroidism occurs when there's a failure of one or more constituents of the calcium homoeostatic mechanisms due to extrinsic factors (Fraser, 2009). Reference values for ionized and total calcium in dogs has been found to be 1.35 ± 0.05 mmol/l and 2.42 ± 0.18 mmol/l, respectively (Szenci *et. al.,* 1988). Parathyroid hormone (PTH), secreted from the parathyroid glands is crucial in the regulation of ionized calcium, keeping it within physiologic limits. PTH responds to changes in circulating ionised calcium via the calcium-sensing receptor (CaSR) located on the surface of the chief cells of the parathyroid gland (Fraser, 2009).

The CaSR responds to a decrease in plasma ionised calcium by increasing secretion of parathyroid hormone, thereby resulting in a compensatory mechanism to restore normal function (Fraser, 2009). The compensatory process acts through three basic mechanisms to help restore plasma calcium back to normal values: receptor-mediated reabsorption of calcium from renal filtrate passing through the kidney tubules; stimulation of osteoclast resorption from bones and other skeletal structures; and increased activity of renal 1 hydroxylase, which results in the production of 1, 25-dihydroxyvitamin D that ultimately increases calcium absorption via the gastrointestinal system (Fraser, 2009).

Should a combination of these effects lead to a reduction in circulating calcium back to normal physiologic values, a feedback loop is triggered on the CaSR, decreasing secretion of parathyroid hormone (Fraser, 2009). Failure of this normal auto regulatory process leads to excessive production of Parathyroid hormone which exerts its toxic effect in causing the accumulation of calcium salts in renal tubules, causing kidney damage over time (Rusenov *et. al.,* 2009).

Clinically important renal osteodystrophy is rarely reported in dogs and cats (Rusenov 2010). However, in a study on feline chronic renal failure, where about 80 cases were diagnosed between 1992 and 1995, renal osteodystrophy was found in about 25 percent of cases presented with end stage chronic renal failure (Barber and Elliot, 1998).

Osteopenic disturbances and proliferation of fibrous connective tissues which is more evident in the jaw and maxilla bones are hallmarks of fibrous osteodystrophy (Bandarra *et. al.,* 2011). One theory for the higher incidences of expression in neonates is because the developing bones are more susceptible to the deleterious effects of hyper-parathyroidism. It's not known why skull and jaw bones are the most affected, being demineralized to such a degree as to cause the rubber jaw syndrome (Rusenov *et al.,* 2009).

Successful management of clinical osteodystrophy involves the control of serum phosphate and calcium along with the use of Vitamin D analogues (Keith, 1998). The use of a low-phosphate diet, though dietary restrictions and use of phosphate binders has been advocated such as calcium carbonate and calcium acetate (Keith, 1998). For patients with end-stage renal osteodystrophy, deficiency in calcitriol result

in calcium malabsorption from the gut. Extra-nutritional sources of calcium should be provided to maintain calcium levels at higher than normal values, to compensate for the increased phosphate levels in serum. Vitamin D analogues and preparations (alfacalcidol, dihydrotachysterol, calcifidiol etc.) have been used to treat secondary hyper-parathyroidism and to correct deficient and endogenous production of 1, á 25-dihydroxy-cholecalciferol (Keith, 1998).

Despite these advances however, osteodystrophy remains a common complication of end-stage renal failure, and continues to pose diagnostic and therapeutic dilemmas for clinical nephrologists (Vardhan and Hutchinson, 2009).

History

The presented case of fibrous osteodystrophy was that of a four years old male Rottweiler dog weighing19 kg, by name Tom-tom. The dog owned by a private owner from Magodo area of Lagos state, Nigeria. The dog was referred to the Small Animal Clinic of the Veterinary Teaching Hospital, University of Ibadan from a private Veterinary clinic in Lagos. The dog was presented with the history of increased thirst, frequent and prolonged urination, anorexia, weight loss and a general weakness. The Owner noticed a bilateral swelling of upper jaw about a month ago, difficulties in eating and chewing of food, epistaxis, haemoptysis, vomiting and dyspnoea. The dog was first diagnosed to be having scurvy or periodontitis by the clinician that was handling the case .The dog was treated with Vitamin C and Erythromycin. The swelling however did not regress after the treatment; rather the clinical manifestations became worse with profuse bleeding from the mouth before it was referred to the teaching hospital.

Clinical examination

On examination, the dog was observed to be markedly emaciated, with obvious bone prominences. The skin has lost its turgor and the mucous membranes were slightly pale. The eyelids were constricted, few ticks observed on the skin and in the ears, but stringy saliva was observed drooling from the mouth. The animal was reluctant to move and did not tolerate exercise. The results from the clinical examination showed rectal body temperature of 38.9°C, heart rate of 130 beats per minute and respiratory rate of 13 per minute and the pulse rate of 124 per minutes. On auscultation, heart tones were clear and normal. Bilateral swelling and deformity of skull bones were observed. The auscultation of lungs revealed no abnormal findings. When palpated, swollen gum was firm and smooth, although the teeth were markedly mobile, weak and shaky. The appetite was good but chewing was difficult. The faeces were dark-coloured and foul smelling. The urination was frequent and urine was clear, colourless, with low specific gravity (1.012). On abdominal palpation, the dog did not show tenderness.

Radiograph revealed an increased transparency of jaw bones, thinned cortices and lacking alveolar bone plates. The roots of teeth were clearly visible.

Haematological findings revealed a moderate non-regenerative anaemia and

mild leucopenia as evidenced by the leucogram result (Table I).

Blood biochemistry revealed hypocalcaemia, marked hyperphosphataemia and high blood creatinine and urea levels (mild azotaemia) when compared to the reference values, there is also mild hyper-bilirubinaemia, and all other analytes show no significant deviation from reference values (Table II).

Cytology

The fine needle aspirate from the swollen gum was bloody. There were numerous inflammatory cells predominantly neutrophils. There were discrete oval to spindle shaped cells with red cytoplasmic granules.

These cells showed considerable pleomorphism. There are also numerous multinucleated giant cells.

Treatment

The dog was on dextrose saline infusion to rehydrate the dog and correct the electrolyte and metabolic disorders while the laboratory investigations were being carried out and but it was found dead in the boarding facility of the hospital, few days after it was presented. Necropsy findings are as shown below.

Gross pathology

The dog was severely dehydrated (sunken eyes, dry carcass and loss of skin elasticity). The hair coat was very rough and the skin infested with ticks. The entire left side of the animal was soaked in urine and the wet skin peeled off easily (urine scalding).

The ocular mucous membranes were markedly pale (paper white). The carcass was severely emaciated (low body weight

Plate 1. The dog on presentation

Table I. Haematology

Parameter	Unit	Value
Packed cell volume	(%)	15
Plasma colour		Normal
Plasma protein	(gldl)	200
Fibrinogen	(mg/dl)	200
White blood cell	(n/ul)	6000
Differential	(%)	Absolute(n/ul)
Seg Neutrophil	81	5346
Band Neutrophil	2	132
Lymphocyte	10	660
Monocyte	5	330
Eosinophil	2	132

Table II. Clinical chemistry

Analytes	Unit	Value
Albumin	g/%	30
Phosphate	mmol/L	7.05
Calcium	mmol/L	1.50
ALT	u/l	121
ALP	u/l	132
AST	u/l	13
Bilirubin	mg/dl	0.8
Creatinine	mg/dl	2.0
Urea	mg/dl	36

and prominent ribs and bony protuberances). The tongue hanged out of the mouth and the anterior – third (1/3) of the tongue was necrotic and greenish.

The oral cavity contained dirty foul smelling pasty materials, some of which formed pseudo membranes in the pharynx and anterior oesophagus.

The gums were markedly swollen on both sides of the upper jaw. The swelling was more marked in the region of the premolars. The gum tissue between the cheeks and teeth were more affected. The swelling was firm to hard and had a smooth surface. The swelling caused mal-positioning of the premolars. A focus of necrosis and calcification was visible on the surface of the lower jaw. Gritty sound was elicited while cutting through the swelling. The lower jaw was malleable with brittle soft bones.

The entire carcass was slightly jaundiced. There was hypostatic congestion of the left lung. A few hard fine substances were scattered throughout the entire lung tissue. The ventral border of the right middle lobe of the lung was emphysematous.

The left ventricle was markedly thickened and both ventricles contained large quantity of chicken-fat clots.

The spleen was shrunken and small in size. The liver was slightly yellow. Both kidneys were small, firm with numerous whitish specks spread throughout the cortical surfaces.

The stomach was rough and leathery. There was a localised mineralisation of the junction between the cardia and the fundus (~7cm) along the smaller curvature of the stomach.

Tentative disease diagnosis

A tentative diagnosis of Osteodystrophia fibrosa (renal rickets) was made based on the above findings.

Plate 2. Picture of the swollen gum and upper jaw with loose teeth

Plate 3. Lateral view of the swollen and cyanotic gum, buccal wounds, loose teeth, pale tongue and palate

Plate 4. Swollen gum with buccal wound, cyanotic mucus membrane on the gum and loss teeth

Plate 5. Picture of the kidney; smaller than normal, congested and having many whitish nodules and necrotic foci.

Plate 6. Lungs in situ, collapse with gritty consistency when cut through

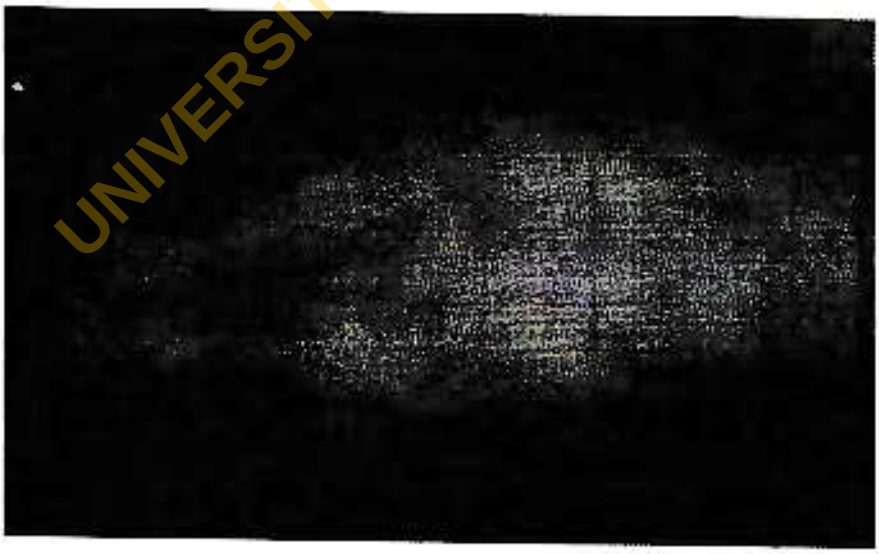

Plate 7. Radiograph: Dorso ventral view showing the swollen muscle mass and pathological changes observed in the maxilla of the dog

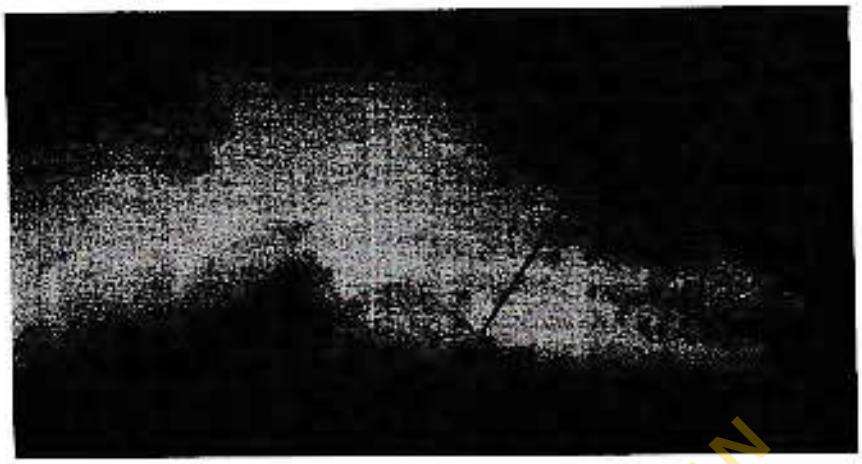

Plate 8. Radiograph: lateral view showing the increased transparency and changes in the jaw bones

Microscopic Examination of the Kidney, Stomach and Gum Sections

This revealed diffuse fibrosis of the renal parenchyma with exaggeration of the interstitium by fibrous connective tissue. Focal lymphocytic infiltrations of the interstitium with extensive tubular necrosis with some of the tubules in the medulla containing protein casts. Some of the glomeruli and tubules showed calcification. Many of the glomeruli and tubules are filled with refractive crystalline materials.

There was severe necrosis of the stomach mucosa with infiltration of the mucosa with neutrophils, lymphocytes and plasma cells. There is also extensive calcification of the submucosa with hyalinisation of the wall of blood vessels in the sub mucosa.

There was abundance of collagen and fibrous connective tissue and osseous material form the ground structure. Some parts of the section are necrotic and calcified. A mixture of thick fibrous connective tissue mixed with osteoblasts. Giant cells were seen scattered throughout the section.

Morphological Diagnosis: Chronic renal failure / Renal Fibrous Osteodystropy

Final Diagnosis: Uremic renal failure with Osteodystrophia fibrosa (Renal rickets)

Discussion

Parathyroid hormone (PTH) is a polypeptide that enhances osteoclastic activity; it enhances bone resorption and releases calcium and phosphates into the blood. Osteoclasts do not possess receptors for PTH whereas osteoblasts do, however the activation of the former is only possible in the presence of the latter (Almanden *et al.*, 1996, Capen and Martin,1977).

In chronic renal failure, the production of 1, 25-dihydroxy- cholecalciferol in kidneys is reduced, leading to slower

intestinal transport of calcium and occurrence of hypocalcaemia (Capen, 1992, Cook and Lothrop, 1994, Martinez *et al*, 1997). For maintenance of calcium homeostasis, an enhanced resorption of calcium from bones occurs. (Bamber and Elliot, 1998), and the released mineral bone substances are replaced with immature fibrous connective tissue (Chew and Nagode, 1994, Lemiex *et al.*, 1990).

Relative or complete deficiency of calcitriol had been assumed to have a primary role in the development of secondary renal hyper-parathyroidism (Chew and Nagode, 1993; Martinez *et al.*, 1997). Calcitriol, the active form of vitamin D, is formed by 1-á-hydroxylation of 25-hydroxycholecalciferol in the cells of renal tubules (Slatopolsky *et al.*, 2005). In the beginning of the CRF, the hyperphosphataemia inhibits renal tubular 1-á-hydroxylase activity and limited calcitriol synthesis (Takahashi *et al.*, 2002; Garcia-Rodrigues *et al.*, 2003). PTH stimulates the activity of renal 1-á- hydroxylase and calcitriol formation. On its turn, calcitriol inhibits PTH synthesis by a negative feedback mechanism (Nagode *et al.*, 1993). In more advanced renal failure, only serum calcium correlates with serum PTH activity (Kates and Sherrard, 1997).

Low serum calcitriol and reduced intestinal calcium absorption has probably a crucial role in hyperparathyroidism occurring in dogs and cats with advanced renal failure. Barber and Elliott (1998) reported that over 50% of cats in the final stage of CRF were hypocalcaemic.

In dogs, skull and mandibular bones are most vulnerable and most severely affected by demineralization and could be changed to an extent such that teeth are mobilized and the mandible bends without fracturing ("rubber jaw" syndrome) (Chew and Nagode, 1993, Keith, 1993). Pathological fractures are rarely seen in dogs and cats with chronic renal failure (CRF) (King *et al*, 1992). Other clinical manifestations of renal osteodystrophy include skeletal demineralisation, bone cysts, bone pain and stunted growth. Bone decalcification and secondary pathological fractures are usually observed in advance stages of CRF (Bamber and Elliot, 1998).

The diagnosis of osteodystrophy fibrosa and secondary renal hyperparathyroidism is based on clinical signs, radiological findings for facial bone demineralization, haematology and serum chemistry analysis indicating a chronic renal failure. The increased serum PTH concentrations, hyperphosphataemia and low total calcium levels established in this clinical case are common findings (Mitch and Walser, 1991, Chandra *et al.*, 1988). We also observed the typical signs of CRF as vomiting, dehydration, polydipsia and polyuria.

From the point of view of differential diagnosis, some neoplastic conditions that can cause swelling of jaws should also be considered. Such tumours of the oral cavity in adult dogs include fibrosarcoma which is more common in large dog breeds, axial osteosarcoma and the papillary squamous cell carcinoma that is commonly encountered in puppies (Feldman and Nelson, 1987). It is however less probable that the swelling is neoplastic, considering the symmetry of the swellings and evidences of chronic renal failure.

The case reported is a contribution to the clinical and laboratory database of canine fibrous osteodystrophy due to chronic renal failure and secondary hyper-parathyroidism.

The observed osteodystrophy with secondary renal hyper-parathyroidism was associated with hyper-phosphataemia, reduced serum calcium levels and decreased bone resistance against the calcaemic effect of PTH. The observed severe anaemia agreed with the findings of Eschbach *et al.* (1990) and Nissenson *et al.* (1991) in their work on dogs and cats with CRF. Erythropoietin deficiency is believed to be the main cause of hypoproliferative anaemia in men and animals with CRF (Nissen-son *et al.* 1991; King *et al.* 1992). Other clinically important causes for anaemia in dogs and cats with impaired renal function are iron deficiency, chronic gastrointestinal bleeding, reduced survival of erythrocytes and decreased glutathione level (Chandra *et al.*, 1988; Cook and Loth-rop, 1994).

The azotaemia observed in this and other studies, is a result of reduced ability of kidneys to excrete protein catabolic products due to considerable destruction of renal glomeruli and decreased glomerular filtration rate (Bovee, 1984 and Mitch and Walser, 1991).

Metabolic acidosis is a common clinical manifestation in CRF and it results mainly from the limited capacity of damaged kidneys to excrete hydrogen ions and secondarily, from disturbance of ammonia production, reduced excretion of phosphates and sulphates, the loss of bicarbonates and the reduced secretion of protons from renal tubules (Kimmel, 1998). Metabolic acidosis has been incriminated as the cause of anorexia, nausea, vomiting, lethargy, weakness and weight loss observed in dogs with CRF (Lemieux *et al.*, 1990; Lulich *et al.*, 1992).

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