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CASE REPORT

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Long-term survival in a dog with unresectable appendicular osteosarcoma treated with zoledronic acid plus carboplatin as palliative care

Sobrevida a longo prazo em um cão com osteossarcoma apendicular inoperável tratado com ácido zoledrônico e carboplatina como cuidado paliativo

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ABSTRACT: Osteosarcoma (OSA) is the most common bone tumor in dogs. It is highly aggressive, and most patients die due to metastasis, especially to the lungs. This report showed the palliative care of an unresectable appendicular OSA in a 10-year-old neutered male Labrador Retriever dog. Amputation of the affected limb was not indicated due to obesity and bilateral hip dysplasia. For this reason, palliative care with carboplatin and zoledronic acid was proposed. The treatment was well tolerated and the owner reported improvement in the lameness and pain, resulting in a good quality of life. A survival time of 30 months (910 days) was observed. Treatment with zoledronic acid and carboplatin may be considered in cases of unresectable appendicular OSA because this treatment was safe and well tolerated.

Keywords: bone tumor; bisphosphonate; canine.

RESUMO: Osteossarcoma (OSA) é o tumor ósseo mais comum em cães. Trata-se de uma neoplasia altamente agressiva, sendo que a maioria dos pacientes vai a óbito devido à ocorrência de metástases, especialmente pulmonares. Este relato descreve o cuidado paliativo de um OSA apendicular inoperável em um cão da raça Labrador Retriever, macho, castrado, de 10 anos de idade. A amputação do membro acometido não foi indicada devido à obesidade e à displasia coxofemoral bilateral. Por esse motivo, foi proposto um tratamento paliativo com carboplatina e ácido zoledrônico. O tratamento foi bem tolerado e o tutor relatou melhora da claudicação e da dor, resultando em boa qualidade de vida. Foi observado um tempo de sobrevida de 30 meses (910 dias). O tratamento com ácido zoledrônico e carboplatina pode ser considerado em casos de OSA apendicular inoperável, uma vez que este tratamento se mostrou seguro e bem tolerado.

Palavras-chave: tumor ósseo; bifosfonato; cão.

INTRODUCTION

Osteosarcoma (OSA) is the most common bone tumor in dogs, accounting for 85% of all skeletal tumors. It is highly aggressive, and most dogs die due to lung metastasis. (Poon; Matsuyama; Mutsaers, 2020; Wycislo; Fan, 2015). OSA mainly occurs in middle-aged to older dogs (7-10 years) in large and giant breeds, with Rottweiler, German Shepherd, Boxer, Doberman Pinscher and Irish Setter among the breeds that are overrepresented (Tuohy *et al.*, 2019). Treatment for OSA can include amputation of the affected limb or resection of axial lesions and adjuvant chemotherapy (Simpson *et al.*, 2017). Amputation is indicated, even for patients with metastasis, to relieve pain (Edmunds *et al.*, 2021). However, underlying orthopedic issues or neurologic disease may preclude amputation due to compromised ambulation. For these reasons, a palliative approach with the use of chemotherapy, radiotherapy and/or bisphosphonates (BPS) may be indicated (Ringdahl-Mayland; Thamm; Martin, 2022; Simpson *et al.*, 2017; Spugnini *et al.*, 2009; Suva *et al.*, 2021; Szewczyk; Lechowski; Zabielska, 2015).

BPs (e.g., zoledronic acid or pamidronate acid) are synthetic analogs of pyrophosphate with a high affinity for bone mineral. It is a family of drugs characterized pharmacologically by their ability to inhibit bone resorption and pharmacokinetically by similar absorption, distribution, and elimination (Suva et al., 2021). BPs are widely used in small animal veterinary practice to treat cancer-associated hypercalcemia and bone pain (Ringdahl-Mayland; Thamm; Martin, 2022; Suva et al., 2021;). In vitro studies have shown that zoledronic acid has antitumoral effects of in both human and canine OSA cell lines, including decreased cell growth, a dose-dependent increase in apoptosis, alteration of the cell cycle distribution, inhibition of tumor cell invasion, and antiangiogenic effects (Iwaki et al., 2024; Liu et al., 2021; Poirier et al., 2003; Suva et al., 2021; Wang et al., 2020). However, its effect on the progression of bone lesions or prevention of metastasis remains unclear (Ringdahl-Mayland; Thamm; Martin, 2022; Smith et al., 2023). The present report describes the use of carboplatin and zoledronic acid as palliative care for unresectable canine appendicular OSA, resulting in long-term survival.

CASE REPORT

A 10-year-old neutered male Labrador Retriever dog, 61

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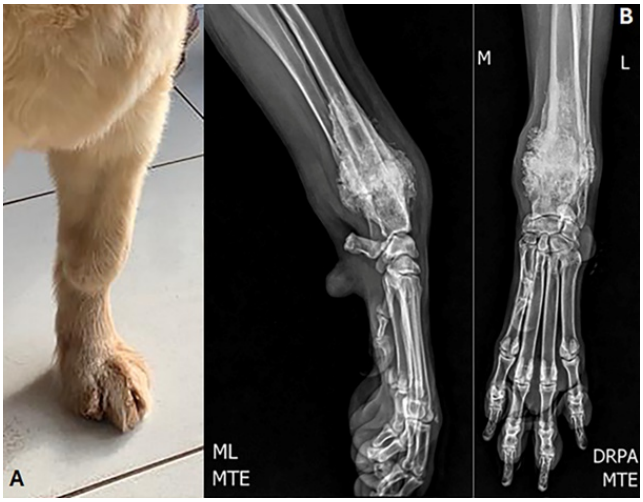
kg, was referred to the veterinary clinic VittaVet (Sales Oliveira, SP, Brazil) with a history of lameness for one month. On physical examination, swelling was observed on the topography of the left distal radius with local pain (Figure 1A). Physiological parameters, such as the respiratory rate, heart rate, pulse, and rectal temperature, were within the normal ranges for the species. Analysis of hematological and biochemical profiles (alanine aminotransferase, alkaline phosphate, albumin, urea, creatinine, total calcium, phosphorus) was unremarkable. Radiography of the left limb revealed cortical lysis, periosteal bone proliferation and soft tissue swelling in the metaphysis of the radius, suggesting a possible bone tumor (Figure 1B). A three-view thoracic radiographic study and abdominal ultrasound did not reveal any abnormalities.

Figure 1 – The dog swellings in the topography of the left distal radius (A). Craniocaudal and mediolateral radiographs of the left radius and ulna. Note the cortical lysis and periosteal bone proliferation, suggesting potential bone tumors (B).



Open bone biopsy with general anesthesia was proposed. Multiple fragments of the lesion were collected, fixed with neutral-buffered 10% formalin and submitted for routine histopathology. On histopathology, atypical osteoblasts characterized by hyperchromatism and increased nuclear volumes were observed. The mitotic count was 1 mitosis per 10 high-power fields. Abundant production of partially mineralized osteoid matrix was observed between the neoplastic cells, confirming osteoblastic OSA.

Amputation of the affected limb was not indicated since the patient presented obesity (body condition score 9/9) and presented bilateral hip dysplasia. These conditions would lead to low functional adaptation, impairing quality of life. The intervention consisted of palliative care with conventional chemotherapy such as carboplatin (300 mg/m^2 intravenously [IV] every 3 weeks, six sessions, then, once monthly in a continuous regimen), zoledronic acid (4 mg/dog IV every 3 weeks), meloxicam (0.1 mg/kg, *per os* [PO] once daily), codeine (0.3 mg/kg, PO, twice daily), gabapentin (15 mg/kg, PO, twice daily) and weight management support for weight reduction. The dog had a complete blood cell count (CBC) and a biochemical profile checked before each acid zoledronic and carboplatin infusion. No adverse effects were observed during the entire treatment schedule, but hyporexia developed during the four days after each cycle of carboplatin, in which the adverse effects were categorized as a gastrointestinal grade 2 by the Veterinary Cooperative Oncology Group (VCOG) (Leblanc *et al*., 2021). Abdominal ultrasound and limb and thoracic radiography were performed every three months during the first year of follow-up and then every six months. After three months of treatment, local tumor control with stable disease was categorized according to the VCOG (Nguyen *et al.*, 2015), and the local tumor control lasted for the entire treatment period. The owner reported improvement in the lameness, pain, and a good quality of life, demonstrating satisfaction with medical therapy.

At 30 months of treatment, the dog was hospitalized and presented anorexia, lethargy, fever, tachycardia, tachypnea, and pale mucous membranes. On admission, the dog was found to have anemia, leukocytosis, neutrophilia with a left shift, an increase in alkaline phosphatase, hyperglycemia, hyperchloremia, hypernatremia and metabolic acidosis. A SNAP 4Dx plus test for infectious disease was performed and was negative. The hematology and biochemistry findings can be observed in Table 1.

Thoracic radiography was unremarkable. Abdominal ultrasound revealed hepatomegaly with a heterogeneous parenchyma and mixed echotexture, in addition to a heterogeneous mass, with a size of 6.34 x 3.8 centimeters, that was observed in the left lateral hepatic lobe. Intensive care treatment with ceftriaxone (30 mg/kg IV twice daily), meloxicam (0.1 mg/kg, PO once daily), dipyrone (25 mg/kg IV three times a day), tramadol chlorhydrate (4 mg/kg IV three times a day) and intravenous fluid therapy (Lactated Ringer's solution) was administered. However, the dog's clinical condition worsened, and he died two days after hospitalization with suspected systemic inflammatory response syndrome (SIRS). The owner did not authorize necropsy for further evaluation, and the dog achieved a survival time of 910 days.

DISCUSSION

Appendicular OSA is a highly metastatic tumor, and most patients will have undetectable micrometastatic disease at the time of diagnosis, with one-year survival rates less than 45% (Frimberger; Chan; Moore, 2016). In contrast with inoperable tumors, these inoperable tumors may have a worse prognosis (Selmic *et al.*, 2014; Duffy *et al*., 2018). For those cases, radiotherapy and chemotherapy are commonly proposed, aiming for local disease control and pain relief (Nolan *et al.*, 2020; Norquest *et al*., 2022).

The progression-free survival (PFS) rate remains poor for patients with unresectable OSA, and the benefit of adding chemotherapy to radiotherapy is still unknown. The median survival time was not significantly different for patients who received metronomic lomustine (184 days) and for those who did not (154 days) (Duffy *et al*., 2018). Furthermore, no significant difference was observed between the survival of dogs that received carboplatin in combination with radiation (120 days) and dogs that did not receive chemotherapy (90 days) (Mueller *et al.*, 2005). A previous study identified that the association of radiotherapy with zoledronic acid may be associated with a lower incidence of pathological fractures and extension of survival in dogs (170 days vs. 44 days)

Table 1 – Hematologic values during hospitalization of the patient.

Parameters	D0 (hospitalization day)	D2 (Day 2)	Reference values
Hematology			
RBC (10^6/µl)	3.11	2.4	5.5–8.5
Hgb (g/dL)	6.9	6.0	12–18
Hematocrit (%)	24.6	19	37–55
MCV (fL)	79	79	63–77
MCHC (g/dL)	28	32	31–35
Platelets (10^3/µl)	261	62	180–500
WBC (10^3/µl)	57.685	62.800	6.000–17.000
Metamyelocytes	–	2.512	0–0
Band neutrophils (/µl)	5.192	4.396	0–500
Neutrophils (/µl)	50.186	37.680	3.600–13.800
Lymphocytes (/µl)	2.307	11.932	720–5.400
Monocytes (/µl)	0	4.396	180–1.800
Eosinophils (/µl)	0	1.884	120–1.800
Biochemistry			
Urea (mg/dl)	26	–	15–65
Creatinine (mg/dl)*	1.46	–	0.5–1.5
ALT (UI/l)	64	–	10–88
Alkaline phosphate (UI/l)	323	–	20–150
Calcium ionized (mmol/l)*	1.19	–	1.2–1.4
Lactate (mg/dl)*	1.22	–	0.3–2.0
Glucose mg(dl)*	137	–	74–110
Sodium (mmol/l)*	156	–	142–152
Potassium (mmol/l)*	3.7	–	3.6–5.0
Chloride (mmol/l)*	135	–	111–121
pH*	7.21	–	7.35–7.45
HCO3- (mmol/l)*	11.3	–	18–26
BE (ecf) (mmol/l)*	-15.9	–	-6 – +1.5
pCO2 (mmHg)*	28.6	–	28–44

*EPOC® Siemens system

(Norquest *et al*., 2022). Nevertheless, the antineoplastic efficacy of this association is controversial (Ringdahl-Mayland; Thamm; Martin, 2022).

In the present case, despite the contraindication of surgical treatment due to the patient's comorbidities, radiotherapy was declined by the owner due to costs. Thus, a combination of carboplatin and zoledronic acid has been proposed as palliative care. The dog had improvement of clinical signs, quality of life and long-term survival (910 days). The treatment with zoledronic acid as monotherapy was reported by a previous report and there was an observed improvement of lameness and stable disease that was noted for 16 months in a dog with OSA (Spugnini *et al.*, 2009). In humans, the value of using these types of palliative treatments in the management of the primary disease is unclear, and more compelling evidence is needed for their role in managing metastatic disease (Biteau *et al.*, 2016; Conry; Rodriguez; Pressey, 2016).

The progression of bone tumors leads to osteolysis, which in turn promotes the dissemination of tumor cells. Zoledronic acid inhibits osteoclast function by inducing apoptosis and may be a promising way to treat OSA metastasis (Conry; Rodriguez; Pressey, 2016; Heymann *et al.*, 2005). For dogs, a phase II study with eleven animals evaluated the use of zoledronic acid in the treatment of canine metastatic OSA and identified that it had limited activity as a single agent (Smith *et al.*, 2023). In contrast, our findings suggest that this BP may prolong survival in dogs with macroscopic disease, particularly when it is used in combination with chemotherapy against unresectable primary tumors with no metastatic disease at diagnosis. Although extrapolation of this case report may not be useful for the canine general population, this good result opens new pathways for the evaluation of combined treatments with chemotherapy plus BP for a primary tumor. These results are reinforced by a previous study with mice, in which treatment with zoledronic acid

prevented the formation of osteolytic lesions and metastasis, reduced local tumor growth and prolonged survival. The combination of zoledronic acid and chemotherapy (ifosfamide) was more effective than either agent alone (Heymann *et al*., 2005).

The most clinically important adverse effect of zoledronic acid in humans is acute renal insufficiency. Other common adverse effects are hypophosphatemia, hypokalemia, hypocalcemia, azotemia, diarrhea, and vomiting (Conry; Rodriguez; Pressey, 2016; Smith *et al.*, 2023). For dogs, zoledronic acid appears to be safe and well tolerated after multiple doses, with no adverse events reported after following 79-89% of the cases (Brewer *et al.*, 2022; Lopes *et al*., 2023). Azotemia may be progressive in a small number of dogs and is not associated with the cumulative dose (Brewer *et al*., 2022). Our patient did not develop any adverse effects during the treatment and had normal electrolyte levels (ionic calcium, phosphorus, sodium, potassium), creatinine and urea. It was suspected that the patient's death was due to SIRS and was not related to the treatment.

Limitations include the study design (case report) and the owner's refusal to have the dog necropsied. Therefore, the cause of death has not been confirmed, and the dog could have had liver metastasis, which, despite being uncommon in OSA, presents a poor prognosis (Cesario *et al.*, 2016).

CONCLUSIONS

This case report suggests that palliative care with zoledronic acid and carboplatin may be considered in cases of inoperable canine appendicular OSA, and it appears to be safe and well tolerated. The use of zoledronic acid may provide an analgesic effect and long survival in conjunction with chemotherapy in the absence of metastasis at diagnosis. Nevertheless, our results should be interpreted with caution due to the study design. The role of zoledronic acid and its association with chemotherapy in this setting remain unclear and need further investigation in large-scale studies.

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