The Use of Zoledronic Acid for Solitary Osseous Plasmacytoma in a Dog

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Summary: A 12-year-old neutered male miniature dachshund was presented with intermittent ataxia. Solitary osseous plasmacytoma (SOP) in the 12th thoracic vertebra (T12) was diagnosed based on the results of diagnostic imaging and histopathology. The combination use of zoledronic acid, melphalan, and prednisolone was extremely effective and long term survival could be achieved, however, mandibular osteonecrosis developed as a suspected adverse effect of zoledronic acid 2 years later. This is the first clinical report of an adverse effect of zoledronic acid in a dog with SOP.

Key words: dog, solitary osseous plasmacytoma, zoledronic acid

Introduction

Vertebral plasma cell tumors are rare in dogs, accounting for approximately 8% of primary vertebral tumors[14] and less than 4% of all vertebral tumors[18]. In humans, vertebral plasma cell tumors are divided into two types: multiple myeloma, which is the disseminated disease, and plasmacytoma, which is the rarer solitary plasma cell tumor[2]. A similar situation is reported in dogs and a solitary plasma cell tumor occurring in bone is known as a solitary osseous plasmacytoma (SOP)[18]. In dogs, the clinical manifestations of vertebral SOP include severe spinal pain, urinary incontinence, and neurologic deficits, including paraparesis and paraplegia. Diagnosis of vertebral SOP in dogs through imaging modalities is dependent on radiography, computed tomography (CT), and magnetic resonance imaging (MRI)[9]. Tissue biopsy or fine-needle aspiration (FNA) of vertebral tumors is essential for the definitive diagnosis of vertebral SOP, but presents a surgical challenge if the diseased part of the vertebra is not easily accessible[14].

Reported treatments in dogs include radiation therapy, chemotherapy with prednisone and melphalan[22,23], bisphosphonates as palliative therapy[3,20], and when possible, surgical resection[14]. Bisphosphonates are synthetic analogs of inorganic pyrophosphate and were initially utilized for diagnostic purposes in bone scanning due to their ability to absorb into minerals of the bone. The pharmaceutical use of bisphosphonates has gained wide acceptance in human bone disorders, such
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as osteoporosis and Pag’s disease. Zoledronic acid, a bisphosphonate, acts as an anti-resorptive agent by inducing osteoclast apoptosis and provides symptomatic pain relief in human bone cancer patients. A previous report describes the use of zoledronic acid as palliative therapy in a case of canine osteosarcoma. In dogs, zoledronic acid has been demonstrated to provide significant pain relief in cases of appendicular osteosarcoma. However, in humans there are several cases of adverse effects such as mandibular necrosis associated with bisphosphonates including zoledronic acid. On the other hand, investigations of the side-effects of zoledronic acid in dogs are limited to experimental studies.

This case report demonstrated that the use of zoledronic acid yielded remarkable pain relief for vertebral SOP, but resulted in the development of mandibular necrosis, which was suspected to be a long-term adverse effect of the drug.

Case description

A 12-year-old neutered male miniature dachshund, weighing 5.2 kg, was presented with one-week history of intermittent ataxia. On initial physical examination, the dog had dorsal pain around the 12th thoracic vertebra (T12). Radiographs of the vertebra revealed spondylosis deformans between the third (L3) to fourth (L4) and the fifth (L5) to sixth (L6) lumber intervertebral spaces. Increased radiolucency in T12 was detected on a CT image (Fig. 1).

Symptomatic therapy started with prednisolone (Prednix®: Shionogi & Co., Ltd., Japan; 1 mg/kg PO every 24 hours), a vitamin B1/B6/B12 complex (Neurovitan®: Astellas Pharma Inc., Japan; octothiamine [25 mg], riboflavin [2.5 mg], pyridoxine hydrochloride [40 mg], cyanocobalamin [0.25 mg]; 1/2 tablet PO every 12 hours), and adenosine triphosphate disodium hydrate (ATP®: Nichi-Iko Pharmaceutical Co., Ltd., Japan; 1 mg/kg PO every 12 hours) until the core biopsy of the T12 lesion was performed. The intermittent ataxia gradually improved with these medications. The dog was anesthetized and a biopsy of T12 was performed with a core biopsy needle (JamshidiTM: Nippon Becton Dickinson Co., Ltd.) on day 13. The histopathology of the biopsy was compatible with a diagnosis of malignant SOP (Fig. 2). Additionally, a serum immuno electrophoretic analysis was performed. While abnormal immunoglobulin M (IgM) levels were detected, no L chain was present. Albumin, alpha-1 globulin, alpha-2 globulin, beta-1 globulin, beta-2 globulin, and gamma-2 globulin were found at 37.7%, 1.6%, 4.3%, 13.8%, 22.6%, and 19.9%, respectively. The serum total protein concentration was 7.1 g/dl, and the albumin to globulin ratio was 0.7. These results indicated that the dog had no monoclonal gammopathy. On urinalysis, Bence-Jones protein was not detected. Based on these findings, a plasmacytoma unassociated with multiple myeloma was diagnosed.

The combination of melphalan (Alkeran®: Aspen Japan Pharma, Japan), prednisolone (Predonine®: Shionogi & Co., Ltd., Japan), and zoledronic acid (Zometa®: Novartis Pharmaceuticals Japan) was offered as a treatment option for this dog, but the use of zoledronic acid was declined by the owner due to the possibility of renal dysfunction and mandibular necrosis as potential adverse effects. Melphalan (0.1 mg/kg PO every 24 hours) and prednisolone (1 mg/kg PO every 24 hours) started after histopathological diagnosis on day 26 (Fig. 3). On day 31, prednisolone was reduced to 0.5 mg/kg PO every 24 hours (Fig. 3), but the dosage of melphalan remained the same and dorsal pain recurred with ataxia. The prednisolone dosage was restored to 1 mg/kg PO every 24
hours on day 33 and a vitamin B1/B6/B12 complex was continued. On day 39, dorsal pain and ataxia resolved. Thereafter, prednisolone was tapered to 0.5 mg/kg PO every 24 hours and the dosages of melphalan and vitamin B1/B6/B12 complex remained the same.

No clinical signs developed until day 96. At this point, the owner agreed to the use of zoledronic acid with the expectation of further quality of life improvement. On day 96, zoledronic acid was initiated at 0.2 mg/kg administered over 1 hour intravenously. On day 124 (second administration of zoledronic acid), the prednisolone dose was reduced to 0.25 mg/kg PO every 24 hours and was reduced showing in Fig. 3. Melphalan was also reduced to 0.05 mg/kg PO every 24 hours on day 243. Thereafter, zoledronic acid was administered every 4 weeks. On day 329, after the eighth administration of zoledronic acid, ataxia of both hind limbs and head shaking were observed. A CT scan was repeated, resulting no abnormalities. Clinical signs improved after prednisolone was increased to 1 mg/kg PO every 24 hours for 1 week. Zoledronic acid was administered again on day 406 and gingival hemorrhage was detected on day 413. On oral examination, an epulis-like mass was found attaching to the buccal portion of the left last lower molar (Fig. 4).

A CT scan and core biopsy of the gingival lesion were performed on day 415. The sampled tissue only showed a hemorrhagic foci, collagenous fibers, and necrotic cells; no signs of neoplastic cell proliferation were observed on histopathologic specimen. Prednisolone was tapered again to 0.25 mg/kg PO every 48 hours.

On day 434, the dog had difficulty in eating due to gingival inflammation. The authors decided to stop the administration of zoledronic acid after the 12th treatment, but melphalan was continued thereafter. On day 446, another swelling was detected on the right mandibular gingiva, and the gingival swelling of the left mandible continued to increase in size. Prednisolone (1 mg/kg PO every 24 hours) and amoxicillin (20 mg/kg PO every 12 hours) were prescribed. On day 454, the appetite returned and the bilateral gingival swelling decreased, so prednisolone was reduced to 0.5 mg/kg PO every 24 hours. At this point, the dog developed epistaxis, the gingival swelling relapsed, and reduced bone density of the mandibular body was detected bilaterally on radiographs. On day 482, the swelling was detected on the right mandibular again, prednisolone dose was increased to 1 mg/kg PO every 24 hours again and continued with same dosage thereafter (Fig. 3). A CT scan and a core biopsy of
Fig. 2. A microscopic finding of a core biopsy sample. Cluster of round cell can be seen around irregular bone fragments. Obvious bone matrix and osteoid formation are not evident. Many uniform independent circular cells can be seen on the smear. These cells tend to have a circular nucleus which is extremely maldistributed. Perinuclear halos are also apparent. These findings are consistent with plasma cells on day 13. HE stain, 400X magnification.

Fig. 4. Epulis-like masses were found attaching to the buccal portion of the left last lower molar, right lower premolar, and right canine on day 413.

Fig. 5. Transverse CT image of the lower jaw showing a periosteal reaction around the left mandibular body on day 482.

Fig. 6. Radiograph of the lower jaw. Bone destruction of the right mandible was detected on day 560.

Fig. 7. Soft tissue sloughing away from the bone surface on the right side. The mandibular bone was necrotic on day 737.

Fig. 8. A microscopic finding of core biopsy sample. Bone cells can be seen in the trabecula, but necrosis and sloughing are also apparent. No hematopoietic cells are evident in the bone marrow. Basophilic granules of collagenous fiber and bacterial agglomeration can be seen on day 750. HE stain, 400X magnification.
the mandibular bone were performed again on same day. CT images revealed a periosteal reaction around the left mandibular body (Fig. 5).

After treatment, the mandibular lesion outwardly healed, but on day 560 swelling and pain relapsed. A radiograph of the jaw revealed destruction of the right mandible and was suspected the cause of pain (Fig. 6), then surgical resection of the mandibular lesion was suggested to the owner, but was not agreed. Symptomatic therapy was continued as previously prescribed. Soft tissue started to slough away from the right mandibular surface on day 716, and from the left mandibular surface on day 737 (Fig. 7). On day 743, the right mandible had fractured and the soft tissue had completely sloughed away from the whole bone surface, and the mandibular body was necrotic. These necrotic lesions were resected with bone rongeurs, but no hemorrhage or pain was detected during this procedure. A large number of neutrophils, a small number of macrophages and small lymphocytes were present on cytological specimen. Histopathologically, the sample showed collagenous fibers and osteocytes were necrotized and slough away in the bone trabecula. In the bone tissue stroma, spindle-shaped cells resembling fibroblasts could be seen, but there were no signs of cell proliferation suggesting plasmacytoma or osteosarcoma (Fig. 8). Based on these findings, chronic inflammation of the mandibular bone necrosis was diagnosed. A sample of tissue was submitted for culture and antibiogram analysis. Based on this last test, chloramphenicol (Chloromycetin® Daiichi Sankyo Co., Ltd.; 15 mg/kg PO every 12 hours) was added to the prednisolone treatment. The dog continued to have difficulty eating and a suspected infection originating from the necrotic tissue gradually led to its death on day 753.

Discussion

Solitary plasmacytic tumors originating from soft tissues are referred as extramedullary plasmacytomas, while those originating in bone are referred as SOPs. SOPs have been also reported in dogs and they involve the appendicular skeleton, zygomatic arch, and ribs. Vertebral plasmacytomas are rare. In dogs, they are considered an early stage of neoplasia that slowly progresses to a multiple myeloma. SOP is usually associated with pain and lameness if the appendicular skeleton is affected or with neurologic signs if the vertebral bodies are involved. In the current case, the chief complaint was intermittent ataxia, consistent with vertebral SOP.

The diagnosis of SOP usually requires tissue biopsy and/or FNA. It is also important to evaluate the condition of the whole body starting with a physical examination, complete blood cell count, serum chemistry, radiography, and ultrasonography. If possible, surgery is recommended in combination with radiotherapy for dogs with SOP. If the dog is ambulatory and stable, radiotherapy can be used alone for palliative therapy. MacEwen et al. described two dogs with SOP that were treated by surgical excision only. One was the case with the zygomatic arch involvement, and in the other case with a rib involvement. Surgical excision, radiation therapy, and chemotherapy can be employed for SOP in humans. Rusbridge et al. described two dogs with SOP that were treated with a combination of radiation therapy and chemotherapy with melphalan and prednisolone. After treatment was initiated, one survived for 4 months and the other survived for 65 months. In the current case, melphalan and prednisolone were initially prescribed, similar to the previous reports. Although the dog experienced vertebral pain, the owner declined the use of zoledronic acid for pain management. After the initiation of treatment with these drugs, the dog exhibited a slow course of clinical improvement until day 96. After the initiation of zoledronic acid for pain management, dorsal pain around T12 resolved. This suggests that, in this context, zoledronic acid may have analgesic effects for the pain with osteolysis.

Bisphosphonate-related osteonecrosis of the jaw has been recognized as a potentially serious physical problem in humans since 2003. An experimental study of mandibular necrosis associated with zoledronic acid in healthy dogs was reported on in 2009; therein, it was concluded that reducing the remodeling rate using bisphosphonates may contribute to the pathogenesis of bone matrix necrosis. Other possible mechanism of the bone necrosis might be a direct toxic effect of bisphosphonates on the bone cells, however, detailed mechanism of the bone necrosis subsequent to bisphosphonates treatment in the canine model still remain unclear.

Osteolysis or osteonecrosis of the jaw is usually caused
by pyorrhea alveolaris, bacterial infections, benign/malignant neoplasms\(^5\), and bisphosphonate administration\(^6\), especially in dogs. On the other hand, osteonecrosis of the jaw related with melphalan alone has not been reported, but it is known as a possible complication from corticosteroid therapy, either alone\(^{10}\) or combined with other drugs\(^8\) in the treatment of various diseases in humans. However, with regard to pharmacophysiology, it was unclear whether zoledronic acid administration contributed to mandibular necrosis in the current case.

From these results, zoledronic acid administration may be associated with bone necrosis of the jaw in dogs, as well as humans. Therefore, when using bisphosphonates to treat various diseases in both dogs and humans, attention should be paid to their potential side effects, including bone necrosis of the jaw.

### References