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Metronomic Chemotherapy with Toceranib Phosphate for a Disseminated Histiocytic Sarcoma in a Miniature Schnauzer Dog

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Abstract : A 15-year-old spayed female Miniature Schnauzer was presented for unilateral foreleg lameness and pain. On physical examination, left elbow joint swelling and stiffness were identified. On a computed tomography (CT) scan, a periosteal reaction of the left humerus from the distal metaphysis to the epiphysis and cortical destruction of the medial condyle was observed. Based on blood tests, histopathology, and immunohistochemistry, it was concluded as a skeletal histiocytic sarcoma. Since the patient's pain was not controlled despite application of a fentanyl patch, a left forelimb amputation was decided upon as part of the palliative therapy. Metronomic chemotherapy with toceranib phosphate and pamidronate was initiated. Toceranib was administered for 3 months without the development of any adverse effects except mild neutropenia. However, 3 months after initiating treatment, the toceranib was discontinued due to moderate gastrointestinal disturbances. Over the next 2 months, a left mandibular bone mass and cortical bone destruction in the bilateral tibia and tarsal joint were identified on CT. The patient became unwilling to eat and was noted to have severe skeletal pain. The anorexia and lethargy were progressively worsening and the owner decided to euthanize the patient. A necropsy was performed and the patient was definitively diagnosed with disseminated histiocytic sarcoma based on histopathologic and immunohistochemical analyses. This report describes a Miniature Schnauzer dog with DHS managed with surgical removal and metronomic chemotherapy with toceranib that survived with an improved quality of life for 7 months.

Key words **:** disseminated histiocytic sarcoma, metronomic chemotherapy, toceranib phosphate, tyrosine kinase inhibitor.

Introduction

Canine histiocytic sarcoma (HS) is a malignancy of macrophages and dendritic cells and has an aggressive tumor behavior with extremely poor clinical outcomes (1). They are locally invasive and metastasize to draining lymph nodes. It has been sub-classified in two primary subtypes, localized or disseminated. Localized histiocytic sarcomas (LHS) develop from a single site while disseminated histiocytic sarcoma (DHS) is an aggressive multisystem disease characterized by the presence of multiple tumor masses in several organ systems (7). This distinction has historically been made based upon the number of involved organs affected at the time of diagnosis because the morphology of HS is highly variable and cannot be used to reliably differentiate between the two anatomic forms (2). The localization of HS on presentation is variable, and the organ most commonly involved is the skin, subcutaneous tissues, spleen, lymph nodes, lungs, or liver, together representing 73.5% of cases. Bone and/or periarticular localization accounted for 18.3% of the cases (5).

Dogs diagnosed with DHS have a more aggressive clinical course and a poorer prognosis when compared with dogs with LHS. Due to their aggressive biological behavior, most dogs with HS are euthanized. Dogs with disseminated disease have a median survival time of 4 months even when treated with chemotherapy (5).

Breeds over-presented among dogs diagnosed with HS include Bernese Mountain Dogs, Flat-Coated Retrievers, Golden Retrievers, Labrador Retrievers, and Rottweilers. Although HS can occur in any breed, Miniature Schnauzers have rarely been reported (4,6,17). However, a more recent study suggested that Miniature Schnauzers may considered one of the over-presentation breeds with HS (8).

This report describes a case of DHS managed with surgery and metronomic chemotherapy with toceranib in a Miniature Schnauzer dog.

Case

A 15-year-old spayed female Miniature Schnauzer was referred for unilateral forelimb lameness and pain. On physical examination, left elbow joint swelling and stiffness were identified and the patient exhibited pain when attempts were made to palpate the left leg. Complete blood count and serum chemistry were within the reference range. Appendicular skeletal radiography revealed lysis of the distal medial condyle of the humerus (Fig 1A). Analgesia (carprofen, 22 mg/kg BID) was prescribed at the request of owners. The dog returned in 15 days in poorer condition and forelimb radiography identified more severe osteolysis and additional periosteal reactions compared to the previous radiograph (Fig 1B). Computed tomography (CT) and bone biopsy were performed to iden-

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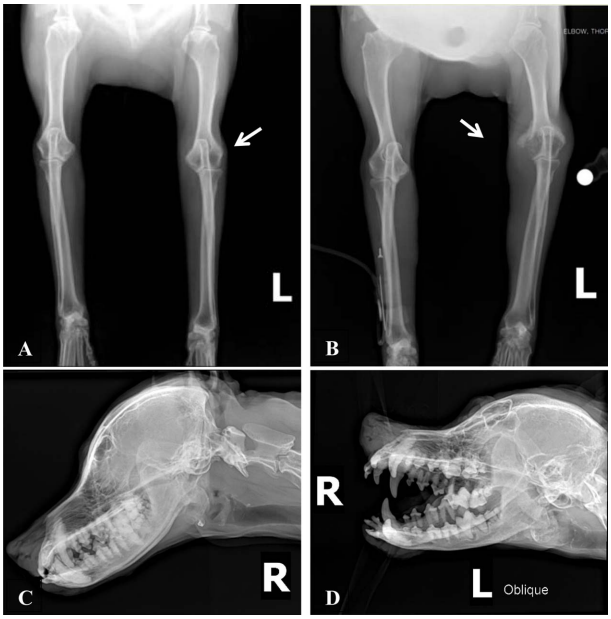

Fig 1. Craniocaudal views of the forelimb and lateral and oblique views of skull radiography (A) Radiograph obtained at initial presentation showing decreased bone opacity in the medial and lateral aspect of the left epicondyle with periosteal reaction. (B) Radiograph obtained 15 days after initial presentation showing a more extensive, permeative and lytic lesion of the left epicondyle compared to the previous view. An active periosteal reaction is present along the supracondylar crest. Lateral (C) and oblique (D) views of the skull obtained 5 months after diagnosis showing the periosteal reaction in the left mandibular bone.

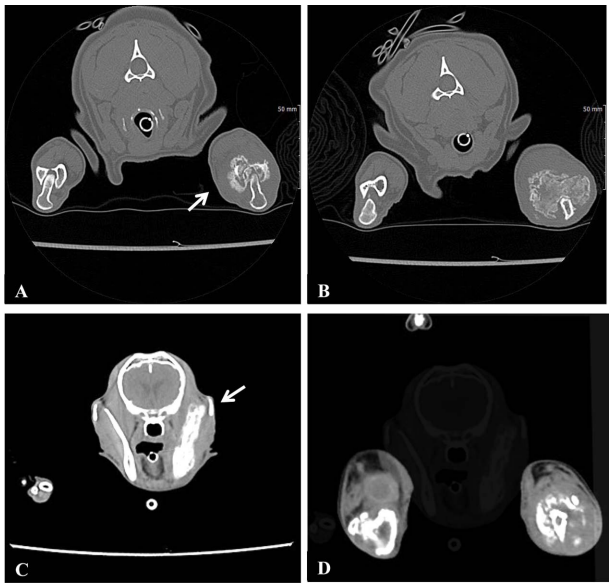

Fig 2. (A) Transverse CT images (15 days after first presentation) showing an amorphous periosteal response with adjacent cortical thinning (arrow) in the distal aspect of the left humerus. (B) Transverse CT images obtained before amputation showing a severe irregular mixed lytic and productive lesion with more extensive and permeative progress in the distal aspect of the left humerus compared to the previous image. (C) and (D) Transverse CT images (right before euthanasia) showing an amorphous periosteal reaction in the left mandibular (C, arrow), bilateral soft tissue edema and cortical destruction with a prominent periosteal reaction (D).

tify the possibility of a tumor and/or metastasis. On the CT scan, a periosteal reaction in the left humerus from the distal metaphysis to the epiphysis and cortical destruction of the medial condyle was found (Fig 2A). The bone lesions were interpreted to represent a bone tumor.

Biopsy samples were submitted to the IDEXX diagnostic laboratory and histopathology revealed an uncapsulated and poorly circumscribed neoplasm composed of undifferentiated, mild anisocytic and individualized round cells (Fig 3A, B). Based on these findings, the tumor was suspected to be a poorly differentiated sarcoma. Immunohistochemistry (IHC) was performed for differentiat diagnosis and it showed the neoplasia cell populations in the sample were positive for CD18. Based on these results, this patient was initially diagnosed with skeletal histiocytic sarcoma.

Palliative treatment was requested by the owner and analgesia was considered. Although a fentanyl patch (25 μg/hr every 3 days) was applied to relieve the pain, the pain was poorly controlled. A left forelimb amputation was performed as part of palliative therapy 2 months post-presentation. A secondary CT scan was performed right before the amputation to identify the progress and extent of the lesions right before amputation and revealed an extensive severe osteolytic and osteoproductive lesion in the left humerus (Fig 2B).

After amputation, chemotherapy options were suggested to the owner. Aggressive chemotherapeutic agents such as lomustine or carboplatin were declined. Metronomic chemotherapy with toceranib phosphate (2.5 mg/kg PO, Monday, Wednesday, Friday (MWF) protocol) and pamidronate (1 mg/kg, per month) were initiated. The patient was reassessed every week. Toceranib was administered for 3 months without the development of any adverse effects except mild neutropenia. During this time, the quality of life of the patient improved and significant progression of the disease was not noted.

However, 3 months after initiating treatment, toceranib was discontinued due to gastrointestinal (GI) disturbances including inappetence and intermittent events of vomiting. One week following discontinuation of toceranib, the patient was noted to have severe skeletal pain including the right hindlimb and several combinations of analgesics such as fentanyl, morphine, gabapentin, carprofen, or tramadol were tried.

Over a 2 month period, a left mandibular bone mass was identified and the patient became increasingly unwilling to eat. Radiography of the skull identified a periosteal reaction in the left mandibular bone (Fig 1C, D). CT abnormalities detected included an aggressive periosteal reaction and cortical bone destruction in the bilateral tibia, tarsal joint, and left mandible and contrast enhancing splenic mass (Fig 2C, D). The patient's anorexia and lethargy were progressively worsening and the owner decided to euthanize the patient.

At necropsy, the following organs were sampled which showed grossly abnormal findings; the mandible, right tibia and stifle joint. Microscopically, the mandible, right tibia and right stifle joint showed undifferentiated neoplastic cells similar to the results of the left humerus and on IHC, the right tibia

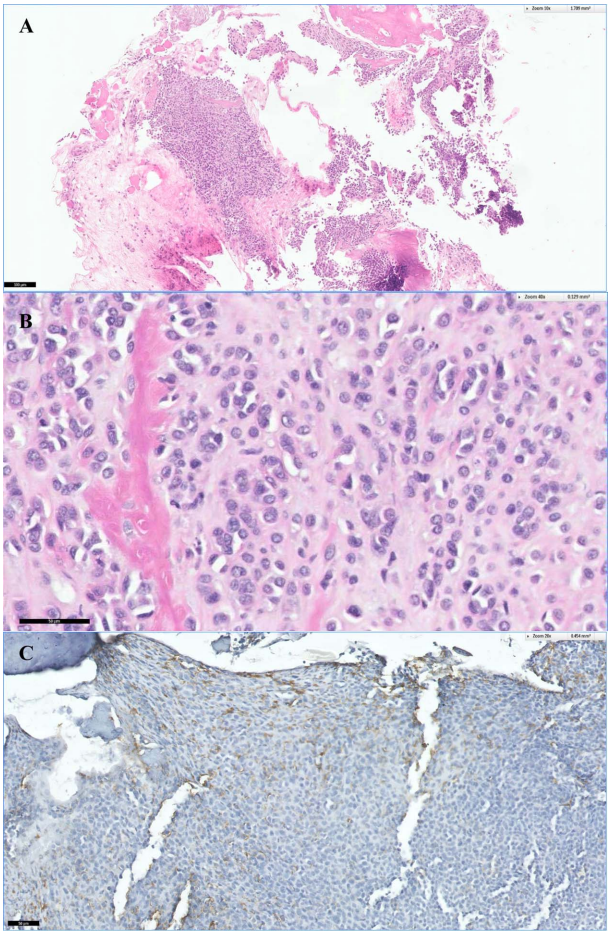

Fig 3. Histopathology. On histopathologic examination, there is a poorly demarcated, unencapsulated, infiltrative, mesenchymal neoplasm (H&E stain). The neoplastic cells are pleomorphic with abundant basophilic cytoplasm (Bar = 100 μm, A, and Bar = 50 μm, B). Immunohistochemistry, showing weak cytoplasmic positivity of neoplastic cells for CD 18 (Bar = 50 μm, C).

was also positive for CD18, which was consistent with DHS.

Discussion

The most common primary bone tumor in dogs is osteosarcoma (OS, up to 85% of cases), and other tumors that involve the bone are chondrosarcomas, hemangiosarcomas, fibrosarcomas, lymphomas, HS and plasma cell tumor (16). Primary bone tumor is suspected based on several aspects such as the anatomical location of the lesion, age, and breed (16). The common sites of OS are the metaphyseal regions of the long bones, the distal radius, and proximal humerus (16). It is extremely rare for OS to be located in bones adjacent to the elbow (1% of appendicular OS) (16). In contrast, DHS is usually located in periarticular bone (60%) that includes the elbow joint in no small rate accounting for 44% of periarticular bone lesions (14). HS should be considered as an additional differential diagnosis in bone tumor presented in atypical location.

The breeds most commonly affected by HS include Bernese Mountain Dogs, Labrador Retrievers, Golden Retrievers, and Rottweilers. In the literature so far, there has been no evidence that Schnauzer is an over-presenting breed, including a quite recently published article that reported only 4 out of a total 180 dogs diagnosed with HS were Schnauzers (5). However, a recently published journal form the USA presented a case series of Miniature Schnauzers with HS and documented over-representation of this breed among dogs with HS in their study population. In Korea, there are only sporadic case reports of various breeds diagnosed with HS.

Palliative treatment and concurrent use of corticosteroids have been suggested as negative prognostic factors, along with disseminated types of HS. Dogs with DHS were reported to be 2.82 times more likely to die when compared with dogs with LHS and dogs with DHS had shorter median survival time of 78 days compared to that of 398 days in dogs with LHS (5).

No effective chemotherapeutic agent is known, although CCNU is recommended predominantly for patients with HS. Toceranib targeting KIT, which is a proto-oncogene, is used in small animal oncology and its efficacy against tumors has been attributed to targeting other molecules such as platelet derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), and epidermal growth factor (EGFR). In dogs affected by histiocytic disease, KIT expression has been evaluated, with no over-expression or KIT mutation found in this species (18). KIT upregulation is also not a common finding in human histiocytic disease (15). However, a recent article revealed that PDGFR expression was present in feline neoplastic histiocytes in 13 out of 15 cases (15). Expression of PDGFR and VEGFR has been demonstrated in histiocytic disease affecting humans and based on the marker profile, several trypsin kinase inhibitor have been used, with some favorable responses (13,15).

The label dose for toceranib (3.25 mg/kg, every other day, EOD) was determined in the initial Phase I clinical trial that established the maximum tolerated dose (MTD) and the dose can be adjusted as needed to address adverse events. Adverse events associated with this regimen included loss of appetite, lethargy, diarrhea, vomiting, weight loss, neutropenia, and lameness (10).

Since the first guidelines were developed, studies of a regimen of toceranib have been conducted. A recent retrospective study demonstrated that significant clinical benefit when toceranib was administered at a median dose of 2.8 mg/kg (11). In a more recent study, dogs with solid tumors that were administered toceranib at an intended dose of 2.5 or 2.75 mg/kg EOD were evaluated and what they found was doses of toceranib ranging from 2.4-2.9 mg/kg EOD provided sufficient drug exposure with substantially reduced adverse events (3). Therefore, based on these recent clinical studies, 2.5 mg/kg EOD was chosen for our patient.

One of the strongest advantages of toceranib is its mild side effects. The most common adverse events of toceranib are GI upset including diarrhea, vomiting, and anorexia. The next most frequent adverse events of toceranib are neutropenia and lethargy (3,11). Comparing with CCNU, which is usually the first recommended chemotherapeutic agent, the degree of adverse effects of toceranib can be minor (12), especially with the doses between 2.4-2.9 mg/kg EOD. Adverse effects have primarily been grade 1 to 2 in nature and in

nearly all dogs resolved with additional supportive medications (3). What these studies suggest is that toceranib is a possible treatment option for HS in dogs.

Our patient survived for about 7 months after initial presentation, including 3 months of treatment with toceranib after amputation of the left leg, which was the initial site of the lesion. During the treatment period, the caregivers were quite satisfied with the quality of life of the patient although ultimately the treatment was stopped because of intermittent vomiting and decreased appetite regarded as grade 1 to 2. Even minor side effects were unacceptable to the owners although supportive medicine was suggested.

In conclusion, we reported a case which described a Miniature Schnauzer with DHS that was progressively affected in three limbs and the mandibular bone but was well managed with toceranib and palliative therapy and survived for 210 days with maintaining quality of life.

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