Case Report Rapport de cas

Treatment of extraskeletal osteosarcoma at a previous injection site resulting in prolonged survival in 1 dog

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Abstract — A rare presentation of an extraskeletal osteosarcoma at a previous interscapular injection site in a dog is described. Treatment included surgical excision of the tumor followed by 6 rounds of intravenous carboplatin, oral toceranib, and cyclophosphamide. The dog survived for 20.5 months after diagnosis despite early development of pulmonary metastases.

Résumé — Traitement d'un ostéosarcome extrasquelettique à un site d'injection antérieur produisant une survie prolongée chez un chien. Ce rapport décrit une rare présentation d'un ostéosarcome extrasquelettique à un site d'injection interscapulaire antérieur chez un chien. Le traitement a inclus l'excision chirurgicale de la tumeur suivie de six séries de traitement de carboplatine intraveineuse, de tocéranib oral et de cyclophosphamide. Le chien a survécu pendant 20,5 mois après le diagnostic malgré le développement précoce de métastases pulmonaires.

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Osteosarcoma is a highly malignant mesenchymal tumor that rarely occurs at extraskeletal sites (1). The diagnosis of extraskeletal osteosarcoma (EOS) relies on the characteristic histopathology of mesenchymal cells with high mitotic index and osteoid or bone production with exclusion of a boney origin of the tumor (2). Extraskeletal osteosarcoma in dogs has been reported to occur in many sites including liver and spleen, gastrointestinal tract, retroperitoneum, urogenital tract, upper respiratory tract, and eye (1,2). In humans EOS are reported to have arisen secondary to trauma. In cats post-traumatic ocular sarcoma and EOS have been reported (3). The pathogenesis of these ocular sarcomas is thought to be due in part to chronic inflammation (3). Additionally, in cats and dogs, injection site sarcomas have been associated with inflammatory reaction due to the injection or possibly the adjuvant and/or other elements of vaccines (4–6).

Extraskeletal osteosarcoma is associated with a poor prognosis with high rates of metastasis at diagnosis (up to 64%). Low median survival times following treatment (26 to 90 d) have been reported in the few available case series (1,2,7). One of these studies in which dogs were treated with curative-intent therapies reported that dogs that received chemotherapy had a significantly lower hazard of death (2).

The purpose of this report was to describe a rare presentation of EOS occurring at a site of prior injection in a dog and prolonged survival associated with curative-intent treatment of EOS.

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Case description

A 6-year-old spayed female Labrador retriever dog was presented to the Veterinary Teaching Hospital, Colorado State University (VTH-CSU), for initiation of chemotherapy for treatment of EOS. Three months before presentation the owner noticed a 3-cm diameter mass in the interscapular region. The dog had a history of injections in this area, including subcutaneous fluids for symptomatic therapy for gastrointestinal signs 1 year earlier and vaccinations 1 to 6 years prior to presentation. On review of the vaccination records for the dog, the site of administration of the vaccine was only consistently recorded for the rabies vaccinations that were administered twice in the region of the right rear limb. The owner reported observing vaccine administration in the interscapular area but this was not documented in the medical record. Other vaccines administered to this dog included inactivated monovalent vaccines (leptospirosis and lyme disease vaccines were administered 2 times each) and multivalent vaccines for distemper, adenovirus, parvovirus, parainfluenza, leptospirosis, and coronavirus (administered at least 3 times). The vaccine manufacturers were not consistently documented in available medical records. An incisional biopsy of the mass was performed and EOS was diagnosed. Staging

tests were performed at that time and included 3-view thoracic radiographs, abdominal ultrasound, and a whole body Tc-99m nuclear scintigraphy bone scan. The results of these tests indicated there was no radiological evidence of a primary osseous tumor site or metastases. A board-certified surgeon with surgical oncology fellowship training performed wide excision of the mass. Histopathology was consistent with EOS with complete margins of at least 2 cm. The histopathology description included identification of adjuvant in both peritumoral macrophages and in transitional areas where osteogenic tumor cells were admixed with a few macrophages containing adjuvant, which were entrapped between irregular deposits of tumor osteoid. Following surgery, a persistent seroma developed at the surgical site. On sampling, the fluid was serosanguinous and cytologic findings were consistent with a surgical site infection. *Pseudomonas aeruginosa* cultured from this sample was susceptible to amikacin and gentamicin. The dog was treated with amikacin (Amikacin; Fort Dodge Animal Health, Fort Dodge, Iowa, USA), 15 mg/kg body weight (BW), IV, q24h for 5 d. While the dog was receiving amikacin treatment, daily monitoring consisted of urine specific gravity, blood urea nitrogen and creatinine, and urine gamma-glutamyl transferase: creatinine ratio. During treatment, there was a mild decrease in urine specific gravity from 1.054 on day 1 to 1.025 on day 5, and blood urea nitrogen increased from 24 to 34 mmol/L [reference range (RR): 6 to 31 mmol/L]. The fluid in the interscapular area was sampled again via ultrasound guidance a week after finishing treatment with amikacin. The second culture showed *Staphylococcus pseudintermedius* susceptible to cefpodoxime proxetil. The dog was then administered a 14-day course of cefpodoxime proxetil (Simplecef; Zoetis, Kalamazoo, Michigan, USA), 6.6 mg/kg BW, PO, q24h. Following this course of treatment, a third culture was taken which showed methicillin-resistant *Staphylococcus* sp. This isolate was susceptible to chloramphenicol. A 21-day course of chloramphenicol (Chlorampenicol; Bimeda, Le Sueur, Minnesota, USA), 41.7 mg/kg BW, PO, q8h, was administered and fluid accumulation resolved.

One week prior to presentation at the VTH-CSU, the interscapular area was assessed with a focused ultrasound examination to resample fluid (7 d after finishing the chloramphenicol) but no fluid was observed. A complete blood (cell) count (CBC) and serum biochemistry performed a few days prior to presentation were normal.

On physical examination at presentation to our institution there was a 20-cm long scar in the dorsal interscapular area from the previous surgery; no other abnormalities were identified. Chemotherapy was prescribed for treatment of microscopic metastases of EOS, consisting of 6 doses of carboplatin (Carboplatin; Hospira, Lake Forest, Illinois, USA), 300 mg/m^2, IV, q3wk. Restaging was performed prior to the 4th and 6th doses of carboplatin, including thoracic radiographs and abdominal ultrasound; there was no radiographic evidence of metastatic disease.

Thoracic radiographs performed 1 month following the 6th dose of carboplatin (6 mo after EOS diagnosis) revealed a suspicious 19-mm diameter soft tissue nodule in the right caudal lung lobe. This nodule was suspected to be a pulmonary metastatic lesion. Two weeks after these radiographs were taken, the dog was presented to VTH-CSU for restaging with a positron emission tomography-computed tomography (PET/CT). No clinical abnormalities were identified on physical examination. A CBC and serum biochemistry performed prior to presentation were normal. The dog was anesthetized for a PET/CT scan with a premedication of hydromorphone (Hydromorphone HCl; Baxter Healthcare., Deerfield, Illinois, USA), 0.1 mg/kg BW, SC, and atropine (Atropine sulfate; Vedco, St. Joseph, Missouri, USA), 0.02 mg/kg BW, SC, and induced with propofol (Propoflo; Abbott Labs, North Chicago, Illinois, USA), 4 mg/kg BW, IV, and midazolam (Midazolam hydrochloride; Hospira), 0.2 mg/kg BW, IV, with maintenance of a mixture of isoflurane (Isoflo; Abbott Labs) and oxygen. Following induction, the dog was transported to the PET/CT scanner, where 3.77 mCi 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) was injected IV. During the FDG uptake period of 1 h, whole body computed tomography (CT) scans were obtained using iohexol (Omnipaque; General Electric Healthcare, Princeton, New Jersey, USA), 770 mg/kg BW, IV, for pre- and post-contrast scans. One hour after the FDG injection, whole body PET images were obtained in multiple bed positions. The PET/CT was performed using a Philips Gemini TF Big Bore 16-slice scanner (Philips Medical Systems Nederland B.V.; Eindhoven, The Netherlands). The main PET/CT abnormalities detected were pulmonary soft tissue attenuating nodules of varying sizes (1 to 17 mm) with varying FDG uptake [Standard uptake value maximum (SUV_{max}) 1.8 to 4.6]. Other abnormalities included a mildly hypermetabolic sternal lymph node (SUV_{max} 2.7) and thickened soft tissue structures between the scapulae with diffuse mild radiopharmaceutical uptake (SUV_{max} up to 2.7). The pulmonary soft tissue nodules were suspected to be metastatic disease but a fine-needle aspirate or biopsy was not performed for confirmation due to the central location and small size of the nodules. The sternal lymph node and surgical site changes were thought to be consistent with reactive changes. No other significant abnormalities were observed.

After the PET/CT, the dog was started on toceranib phosphate (Palladia; Pfizer, New York, New York, USA), 2.75 mg/kg BW, PO, administered on a Monday, Wednesday, and Friday schedule; in combination with cyclophosphamide (Cyclophosphamide; Roxane Laboratories, Columbus, Ohio, USA), 25.0 mg/m^2, PO, and carprofen (Rimadyl; Pfizer), 2.2 mg/kg BW, PO, both administered on alternating days to the toceranib (Tuesday, Thursday, Saturday). A CBC was performed weekly for the first 4 wk after starting these treatments. Serum biochemistry and urinalysis were performed every 4 to 6 wk. No abnormalities were detected.

One month after the PET/CT (9 mo after EOS diagnosis), the dog was presented to VTH-CSU for a repeat thoracic CT for monitoring of pulmonary metastatic disease. The physical examination was unchanged. A CBC and serum biochemistry performed the week prior to presentation were normal. The dog was sedated with medetomidine HCl (Domitor; Zoetis), 0.001 mg/kg BW, IV, and butorphanol (Butorphanol tartrate; Pfizer), 0.3 mg/kg BW, IV, for a thoracic CT. The thoracic CT revealed a small increase in size of the soft tissue nodule in the

right caudal lung lobe (longest diameter 21.2 *versus* 17.2 mm previously) but other nodules were unchanged in size. One additional small 3.8-mm nodule was noted in the left caudal lung lobe and 1 previously noted nodule in the dorsal right caudal lung lobe could not be identified on the repeat thoracic CT. With evidence of stable disease, the toceranib and cyclophosphamide were continued and restaging with thoracic CT and abdominal ultrasound was recommended every 2 to 3 mo.

Three months after the recheck CT (12 mo after EOS diagnosis), a repeat thoracic CT was performed at VTH-CSU using the previous sedation and CT protocol. Thoracic CT abnormalities included a small increase in size of the right caudal lung lobe nodule (27 mm *versus* 21.2 mm) but no other changes of pulmonary soft tissue nodule size or interscapular previous surgical site appearance. Given the changes in the CT findings different options were discussed with the owner including continued oral toceranib and cyclophosphamide, stopping those medications and starting intravenous maximum tolerated dose chemotherapy or considering a different oral tyrosine kinase inhibitor agent. A decision was made to continue with the toceranib and cyclophosphamide treatment, given these were well-tolerated by the dog. Three months following this thoracic CT (15 mo after EOS diagnosis), a full body CT was performed at VTH-CSU for routine chest and abdominal restaging. Abnormalities included a mild to moderate increase in size of all pulmonary nodules (right cranial 7.0 mm *versus* 5.2 mm, right middle 6.6 mm *versus* 3.9 mm, left caudal 4.4 mm *versus* 3.1 mm) and a static appearance of the previous interscapular surgical site. Also a smoothly marginated, wedge-shaped, mildly hypoattenuating, non-contrast enhancing region within the dorsolateral cortex of the right kidney was observed and was thought to represent an infarct. With the progression in size of the pulmonary nodules, changes in treatment were discussed as before. The owner elected not to pursue a change in treatment given the lack of documented efficacy of other treatment options for gross pulmonary metastatic osteosarcoma and the possibility of side effects that could diminish the dog's quality of life. A decision was made to continue the toceranib and cyclophosphamide at previously prescribed doses.

Three months after the recheck CT (18 mo after EOS diagnosis), the dog was presented to VTH-CSU for restaging following development of inappetence, right hind limb pain and lameness. The toceranib was discontinued 1 wk before presentation, due to inappetence. Following discontinuation some improvement in appetite was observed. Tramadol (Tramadol HCl; TEVA Pharmaceuticals USA, Sellersville, Pennsylvannia, USA), 3.5 mg/kg BW, PO q8h, was started for the right hind limb lameness and mild improvement in the lameness was seen. On physical examination, no right hind limb lameness was present and no abnormalities were found on the orthopedic examination that could account for the right hind limb lameness reported. Given the presence of pulmonary metastatic lesions in this dog, bone metastatic disease was suspected to be the cause of lameness. The dog was anesthetized and a PET/CT was performed using the previously described protocols. Abnormalities on the PET/CT included a progression in pulmonary metastatic disease with multiple soft tissue attenuating pulmonary nodules

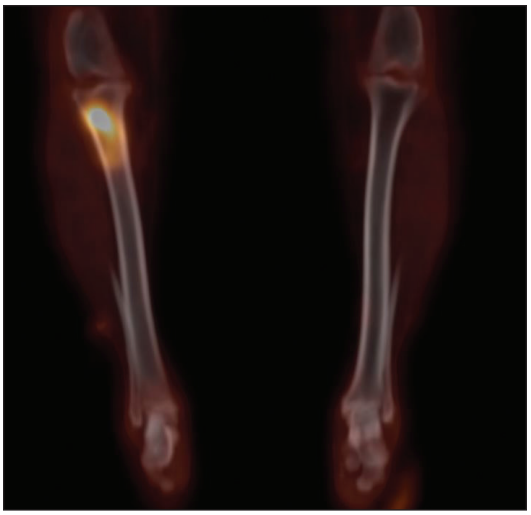

Figure 1. PET/CT reconstruction image showing an intensely hypermetabolic lesion (34 mm, SUV_{max} 9.14) in the right proximal tibial metaphysis.

(right caudal lung lobe nodule 50 mm with SUV_{max} 3.8). A large right caudal lung nodule was resulting in bronchial compression and focal lung atelectasis distal to the nodule. There was also an intensely hypermetabolic lesion (34 mm, SUV_{max} 9.14) in the right proximal tibial metaphysis (Figure 1). The tibial lesion was associated with a mild intramedullary trabecular lysis and was partially demarcated by a poorly defined sclerotic rim. This lesion was consistent with osteosarcoma bone metastasis. The toceranib and cyclophosphamide were discontinued. Masitinib (Kinavet-CA1; AB Science USA, Short Hills, New Jersey, USA) was started at 12.4 mg/kg BW, PO, q24h, and tramadol, 3.5 mg/kg BW, PO, q8h, and carprofen, 2.2 mg/kg BW, PO, q12h were continued.

One-week following the PET/CT, the dog was presented to VTH-CSU for coarsely fractioned radiation therapy of the right tibia for palliation of continued pain and hind limb lameness. Physical examination revealed right hind limb lameness (2/5), but was otherwise unremarkable. Radiation therapy utilized parallel-opposed beams for a clinical setup with the field margins based upon measurements taken from the PET-CT. The dog was anesthetized on 2 consecutive days with propofol, 4 mg/kg BW, IV and midazolam, 0.2 mg/kg BW, IV, with maintenance of a mixture of isoflurane and oxygen. Two 8 Gy fractions of radiation were administered with a Varian Trilogy linear accelerator (Varian Medical Systems; Palo Alto, California, USA) to the right proximal tibial metaphysis. Following radiation treatment, the owner saw a significant improvement in the right hind limb lameness for a period of 6 wk. A few weeks after starting the masitinib, proteinuria was detected, so benazepril (Benazepril hydrochloride; Trigen laboratories, Sayreville, New Jersey, USA), 0.25 mg/kg BW, PO, q24h, was started in an attempt to decrease the suspected drug-induced proteinuria without discontinuation of the mastitinib. Improvement in the proteinuria was noted a week after starting the benazepril.

The dog was presented to VTH-CSU 2 mo after the radiation therapy (20 mo after EOS diagnosis) for worsening right

hind limb lameness and pain. The dog was receiving tramadol, 3.5 mg/kg BW, PO, q8h), gabapentin (Gabapentin; TEVA pharmaceuticals USA, Sellersville, Pennsylvannia, USA), 10 mg/kg BW, PO, q8h, carprofen, 2.2 mg/kg BW, PO q12h, amantadine (Amantadine; Pai Pharmaceutical Associates, Greenville, South Carolina, USA), 3.5 mg/kg BW, PO q24h, buprenorphine (Buprenorphine HCl; Beckitt Benckiser Health Care, Hull, England), 0.01 to 0.02 mg/kg BW, SC, as needed, or fentanyl (Fentanyl citrate; Hospira), 3 to 5 μg/kg BW, intranasal as needed, for additional analgesia. Right tibial radiographs had been performed before presentation and showed a mixed osteoproliferative and osteolytic lesion of the proximal tibial metaphysis with no evidence of pathological fracture. On physical examination, the dog was non-weight bearing lame on the right hind limb; firm swelling was palpated around the right proximal tibia and pain was elicited on palpation of this area. Muscle atrophy of the right hind limb was also present. Blood urea nitrogen and creatinine levels were normal, and no other clinical abnormalities were present. The dog received a repeated protocol of the coarsely fractionated radiation therapy, receiving two 8 Gy fractions on consecutive days. The dog also received pamidronate (Pamidronate disodium; Hospira), 1 mg/kg BW, IV, diluted in 1 L of 0.9% NaCl (0.9% NaCl; Hospira) over 2 h before the second fraction of radiation therapy. Following the second radiation treatment, the dog failed to improve significantly and 2 wk after treatment experienced 2 tonic-clonic seizures. The day of the seizures, the dog was euthanized due to declining quality of life (at 20.5 mo after EOS diagnosis). A necropsy examination was not performed.

Discussion

Development of fibrosarcoma has been reported following injections and associated with microchips in cats and dogs (5,6,8,9). The pathogenesis of injection-site sarcomas in cats and dogs is unclear but it is believed that chronic local inflammation caused by an injection or traumatic incident is the predisposing factor for development of sarcoma at the site in a genetically sensitive host (4). Vaccination with inactivated vaccines containing adjuvant (such as aluminium) has been implicated in causing severe local inflammation resulting in stimulation of malignant transformation of fibroblasts. This relationship between development of sarcoma and presence of adjuvant has been supported by the finding of traces of adjuvant phagocytosed in local macrophages within the inflammatory reaction (5). In dogs, EOS has been reported subsequent to potential inflammation due to retained sponges following surgeries (10–12). In this case there was evidence of inflammatory reaction consisting of macrophages with phagocytosed material that could be consistent with vaccine adjuvant. This is similar to that seen in presumed injection-site fibrosarcoma cases in a study from 2003 (5). To the authors' knowledge this is the first report of EOS in a dog at the site of previous injection. Chronic inflammation due to previous injections or vaccines in the interscapular area could have contributed to tumor development in this dog.

Osteosarcoma of extraskeletal sites is associated with a high rate of metastasis (57% and 64%) (2,7). Monitoring for metastases (restaging) is indicated following treatment of osteosarcoma; commonly used tests include thoracic radiographs, thoracic CT, abdominal ultrasound, full body CT, and full body scintigraphy. Thoracic radiographs were performed initially in this dog due to availability at the referring practice, and because thoracic CT has been shown to have an increased sensitivity for detection of pulmonary metastases for appendicular osteosarcoma (13,14). A PET/CT has not been reported for staging or restaging for osteosarcoma or EOS in dogs but it is used for staging and restaging of human osteosarcoma (15,16). Positron emission tomography utilizing the FDG radiopharmaceutical or tracer can assess for evidence of accumulation of FDG in cells. The FDG tracer will accumulate to a greater extent in metabolically active tumor cells, but can also be increased in inflammatory lesions and muscles inflamed as a result of compensatory weight-bearing (17). A PET/CT has been shown to be more sensitive than bone scintigraphy for detection of bone metastases in human osteosarcoma (18). For this dog, PET/CT facilitated detection of a suspected bone metastasis and assisted in monitoring of metastatic lesions. Detection of the suspected right tibial bone metastasis allowed administration of coarsely fractionated radiation therapy to help treat pain associated with the bone lesion.

It is possible that the infection that developed following surgery in this dog may have contributed to the prolonged survival experienced. Improved survival has been documented in dogs and in humans with osteosarcoma who developed infection after limb-sparing surgery (19–21). The mechanism for this is unknown but has been postulated to be due to up-regulation of antitumor immunity. This could be through cellular or humoral responses to the infection and the effect of the presence of the allograft on the immune response (19). The infections in these studies were associated with allografts; the effect of more superficial soft tissue infections on survival following treatment for osteosarcoma is unknown.

Canine EOS has been reported to have a high metastatic rate at diagnosis and death of 57% and 64%, respectively (2,7). Very few studies have reported treatment of EOS but in 1 study administration of chemotherapy following surgery significantly improved survival (2). With a high reported metastatic rate it follows that administration of chemotherapy to treat microscopic metastases may improve survival. The dog in this report received a course of IV carboplatin, which has been reported for treatment of skeletal osteosarcoma following surgery (22). Development of metastatic disease or tumor recurrence leads to death in most dogs that are treated for EOS (1,2). Following the development of metastatic disease in canine osteosarcoma often the main goals are to decrease pain and maintain quality of life. Following the development of small pulmonary metastases in this dog, a tyrosine kinase inhibitor (toceranib) and cyclophosphamide were administered to try to decrease the rate of progression of these metastases. Toceranib has reported biologic activity against metastatic osteosarcoma (23). Metronomic cyclophosphamide has not been evaluated specifically as a treatment for osteosarcoma metastasis but has been used in combination with IV chemotherapy for canine osteosarcoma and following surgical resection of soft tissue sarcomas in dogs (24,25). This dog developed bone metastases later in the course of disease

that were treated with coarsely fractionated, palliative radiation therapy to decrease pain associated with the bone lesion in the right proximal tibia. A combination of therapy administered following surgical excision of EOS in this dog lead to prolonged survival and maintenance of quality of life as reported by the owner.

This report describes a rare presentation for EOS in a dog at a site of previous injection. With curative-intent treatment of EOS then subsequent treatment of metastatic disease, this dog experienced a good quality of life and prolonged survival.

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