# Bilateral Osteosarcoma Associated with Metallic Implant Sites in Two Dogs

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## ABSTRACT

Osteosarcoma associated with metallic implants is rare in dogs. Several previous case series and case reports of solitary implant-associated osteosarcomas have been published, but none documenting this atypical clinical manifestation of the disease at multiple skeletal sites. Previous cases of osteosarcoma at multiple sites in dogs have been reported, but these were not implant associated. This report uniquely describes two cases of bilateral osteosarcoma likely associated with metallic implants in dogs, and provides a comprehensive review of the relevant literature.

**Key words:** Osteosarcoma; Bilateral; Implant; Dogs.

## INTRODUCTION

Osteosarcoma (OSA) is an aggressive tumor originating from primitive osteoblasts (bone-forming mesenchymal cells). It is the most common primary bone tumor in dogs, comprising up to 85% of all skeletal malignancies (1). Despite the common occurrence of canine OSA, understanding of the disease's less typical clinical manifestations, etiologies, risk factors, and potential preventative strategies remains limited.

The etiology of OSA in any individual dog is likely multifactorial (1).The well-recognized breed predispositions imply a genetic basis, although it is suggested that overall size (height and weight) is a more significant risk factor (1). Because of this, and due to the fact that OSA tends to arise in the major weight-bearing bones adjacent to late closing physes, it is hypothesized that size and growth rate in combination create a stressful biomechanical environment in which cellular damage and microfractures amplify mitogenic stimuli (1). Other identified risk factors include chronic osteomyelitis, osteochondrosis/osteonecrosis, previous traumatic fracture, metallic implants used for fracture repair and Tibial Plateau Leveling Osteotomy (TPLO), and radiation exposure (1). Weaker causal associations are reported for both bone infarcts and bone cysts (1).

OSA, occurring in association with metallic implants, is rare in dogs (2, 3, 4). Two recent retrospective studies (3, 5), as well as several case series and case reports dating back over four decades have described this phenomenon and the estimated occurrence rates (3). However, this manifestation of osteosarcoma remains poorly understood. The two cases documented here differ from those previously reported, because both dogs had bilateral tumors associated with sites of previously placed orthopedic implants.

## CASE REPORTS

### Case 1

A one year-old, castrated male, Mastiff, weighing 50 kg, presented to the hospital with an approximately six-month history of progressive bilateral hind limb deformity, causing hind limb pain and impeding ambulation. On physical examination, bilateral lateral tarsal valgus was obvious, and there was crepitus of the right stifle. Radiographs of both tarsi revealed a minimum of 15° bilateral lateral angulation of the distal pelvic limbs, centered at the distal physes of the cruri. On the right there was also lateral luxation of the patella, cranial displacement of the intrapatellar fat pad, distention

of the caudal joint pouch, and lateral positioning of the tibial tuberosity. A right closing wedge osteotomy and tibial tuberosity transposition were performed using a 7-hole 4.5 mm broad dynamic compression (DCP) plate (Synthes USA, Paoli, PA) seven 4.5 mm cortical screws and three Kirschner wires (Securos Surgical, Sturbridge, MA).

Six weeks later, a left closing wedge ostectomy, tibial tuberosity transposition and medial capsular imbrication were then performed with a 7-hole 4.5 mm broad DCP (Synthes USA, Paoli, PA), seven 4.5 mm cortical screws and two Kirschner wires. Post-operative radiographs on both occasions revealed good apposition of the ostectomy margins, and good alignment of the stifle and tibiotarsal joints. The dog recovered well from both anesthetics, and was discharged the following day with deracoxib (2 mg/kg PO q 24 hr) and codeine (2.4 mg/kg PO q 8 hr), as well as instructions regarding restricted activity and heat packing to reduce swelling.

Two weeks postoperatively following both surgeries, however, the dog was presented to the primary care veterinary clinic with increased soft tissue swelling at the distal incision sites. Infection was suspected clinically, and a two week course of a broad spectrum antibiotic prescribed. Another two weeks following the second surgery, the dog was re-presented to the hospital with persistent swelling at the surgery site. The physical examination findings and radiographic changes were considered consistent with cellulitis and osteoarthrosis of the left stifle. Further analgesia and anti-inflammatories were dispensed, and the dog recovered over time.

Almost seven years later, the dog re-presented to the hospital with a history of reluctance to rise and ambulate, as well as reported drainage from the medial surface of the distal left tibia. Radiographs revealed a spiral fracture of the distal left tibia involving the implant. A right cranial cruciate ligament rupture was also diagnosed. Surgery was performed to remove the previously placed implant from the left hind limb, and the fracture was repaired with a 4.5 mm dynamic compression plate and five cortical screws. The dog was rechecked two months later and, at that time, appeared to be recovering well from surgery as the left tibial fracture was healed and the surgical implants remained in position.

The dog was re-presented almost 12 months later with a history of acute onset inability to rise. Radiographs (Figure 1) of both hind limbs revealed a mixed lytic and proliferative pattern in the distal tibial regions, mostly consistent with either neoplasia or chronic inflammation.

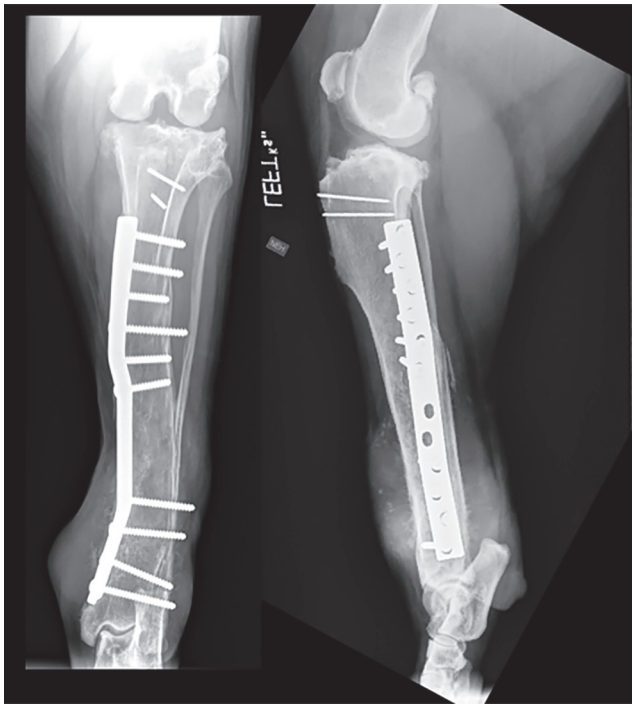

**Figure 1:** Lateral and AP radiographs showing Case 1's aggressive mixed lytic and proliferative lesion of the left distal tibia associated with the previously placed TPLO plate.

Thoracic radiographs taken at that time revealed no overt evidence of pulmonary metastasis. Fine needle aspirates of both sites were performed and the cytologic diagnosis was osteosarcoma (OSA). Tissue biopsies were also performed, with only one being confirmatory. Palliative care, consisting of analgesia and bisphosphonate treatment was commenced. Six months later, the dog was euthanized. Necropsy was not performed in this case.

## Case 2

An eight year-old, spayed female, Great Pyrenees, weighing 46.5kg, was presented to the hospital with a one-week history of mainly right hind limb lameness and pain. Radiographs of the right tarsal region performed one week prior by the primary care veterinarian reportedly revealed changes consistent with OSA. Repeated radiographs confirmed the presence of an ill-defined region of irregular lysis associated with the right distal tibia, with cortical breakthrough, adjacent periosteal reaction and surrounding soft-tissue swelling. There was an extended zone of transition extending proximally between the radiographically abnormal and normal bone. Concurrent radiographs

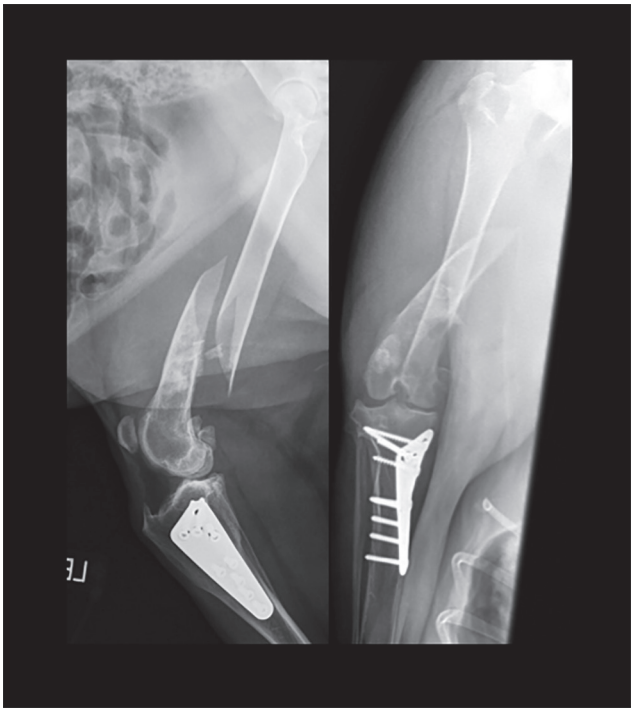

**Figure 2:** Lateral and AP radiographs showing Case 2's long oblique fracture of the left femoral diaphysis, and the extensive region of lysis adjacent to the previously placed TPLO hardware.

(Figure 2) of the left femur revealed a long oblique fracture of the diaphysis, with cranial displacement and override, and a similar region of lysis associated with the distal femoral fracture fragment. There was also incidentally noted joint effusion and moderate degenerative joint disease (DJD) of both stifles. Bilateral tibial plateau leveling osteotomy (TPLO) had been performed 30 months earlier, with a 3.5 mm broad TPLO plates and nine screws per plate (Securos Surgical, Sturbridge, MA). Given the limited therapeutic options available for this patient and the grave prognosis, humane euthanasia was requested by the owner.

Subsequent necropsy revealed gross lesions consistent with osteosarcoma in the right tibia and left femur, and an incidental finding of a mass in the thyroid gland, which was histopathologically diagnosed as a follicular carcinoma. Histopathologic analyses of the skeletal lesions were consistent with OSA at both sites.

## DISCUSSION

The ability of biomaterials, or their breakdown products, to potentially induce cancer is of increasing concern in the rapidly expanding medical device field (15). The use of metallic hardware and other biomaterials for fracture repair, correction of skeletal deformities, biomechanical reconstruction of joints following ligamentous injury, and prosthetic replacement of joints is now routine in contemporary veterinary orthopedic surgery. These procedures effectively restore mobility and enhance quality of life for these dogs. Other implanted devices, such as microchips, stents, and even valves, are also becoming increasingly common in veterinary medicine.

The majority of previously reported implant-associated tumors in dogs are OSAs, occurring in bone at the site of previously placed orthopedic hardware, similar to the two cases presented here (3, 5, 6, 7). Unlike the present two cases, however, none of the previously reported cases occurred bilaterally or at multiple sites.

Interestingly, there is a recent case report documenting four dogs in which bilateral OSAs arose seemingly spontaneously (8). Moreover, it has been previously reported based on nuclear scintigraphy studies that 1.4-28% of dogs diagnosed with OSA have secondary bone lesions at the time of diagnosis (8). It remains unclear, however, whether these multifocal lesions represent early metastatic disease, metasynchronous disease, or truly synchronous neoplasia (8). Such reports confound attempts to prove a direct causal relationship between metallic implants and OSA.

Other neoplastic histotypes have also been reported associated with previously placed orthopedic hardware, including undifferentiated sarcoma, histiocytic sarcoma, fibrosarcoma and malignant mesenchymoma (3, 6, 9, 10, 11).There are also scarce reports of various sarcomas arising at non-osseous soft tissue sites, associated with miscellaneous both metallic and non-metallic foreign objects, including a pacemaker wire, microchip and surgical sponge (12, 13, 14).

Historically, there is a credible body of literature in animal models attesting to a causal relationship between foreign materials and sarcomas (3, 7, 15, 16). Some of the materials previously utilized in orthopedic implants, including cobalt, cadmium, nickel, and various alloys thereof, have been demonstrated to be carcinogenic when tested in rodent models (3, 7, 15, 16).Whilst the materials utilized in contemporary circumstances are generally considered biocompatible and non-toxic, studies have still implied potential oncogenic properties (3, 7, 15, 16).

In addition to the presence of the actual implant material, there also exists the possibility of leaching of trace amounts of residual compounds, utilized during the implant manufactur-

ing process, including monomers, catalysts, plasticizers and antioxidants, and these too are hypothesized to play a role in tumorigenesis (15).

Long-term corrosion and wear debris are also of concern (3, 7, 15). Corrosion occurs with all metallic implants to varying extents, resulting in surface damage that may contribute to an altered host reaction, disrupted cellular activity, chromosomal and genomic aberrations, and carcinogenesis (2, 7, 10, 15). Fretting and crevice formation, and the resultant wear debris, can potentiate these pre-neoplastic changes (4, 7, 17, 18). Once again, although these changes are less likely to occur today, with the less reactive stainless steel and titanium implants, they are not reported with these materials and remain a persistent contemporaneous concern (5, 7).

Concern has been previously expressed regarding the material properties and casting process utilized for TPLO Slocum plates specifically, causing corrosion and resultant adverse biologic effects (4, 5, 17, 18). However, implant-associated sarcomas have been subsequently reported for non-Slocum plates (5). Furthermore, as pointed out by both Sartor and Selmic, the frequency with which cast stainless steel plates were utilized historically compared to wrought stainless steel plates or even titanium may have skewed previously published data and the associated conclusions (4, 5). A recent study found no corrosive issues with Slocum plates (19).

Additional extraneous factors implicated in implant-associated sarcomagenesis include chronic osteitis and/or osteonecrosis at the implant site (3, 4, 7, 10, 16). One theory postulates that the implant acts as a nidus for ongoing inflammation, which in itself is potentially carcinogenic (4, 7).Burton *et al.* reported a 50% complication case post-operatively in the dogs that went on to develop implant-associated OSA (3). It is for this reason, that case 1's disease cannot be attributed solely to the presence of the metallic implants. Case 1 had evidence of chronic intermittent inflammation and possibly infection, most marked on the left side, but also on the right, for several years prior to tumor diagnosis.

Infarction has also been suggested as an independent risk factor for osteosarcoma in dogs (20).There is a single case report in which infarction occurred shortly after total hip arthroplasty in a dog. Osteosarcoma then developed 5 years later, adjacent to the distal site of the infarct, rather than immediately associated with the implant (20). No infarcts were noted in the dogs in the present report.

Despite the aforementioned hypotheses and evidence, and the increasing commonality of procedures, such as the TPLO, in modern-day canine orthopedics, mesenchymal tumors of bone occurring in association with metallic implants remain seemingly rare in dogs, although the actual incidence is unknown (2, 3, 9, 10). Reported incidence rates in dogs for OSA associated with fracture repair are estimated at between 1.0-4.5% of all cases of OSA (2, 9, 10). This estimation is based on three studies that attempted to demonstrate causality and/or associated risk between fracture repair incorporating metallic hardware and OSA, but failed to find statistical significance (9, 10). A more recent and statistically robust study calculated the relative risk of OSA following fracture repair, and compared it to the relative risk of OSA following open reduction for joint luxation, which is not a recognized risk factor for OSA, both were similar (2). The reported incidence of 0.0008% in this study was miniscule, even compared to previous estimations and notably less than the incidence of OSA in predisposed breeds (0.005-0.15%) (2). Another recent and statistically validated study evaluated the incidence rate of OSA following TPLO specifically (4), in light of an earlier abstract reporting the risk as 0.075% The reported incidence density rate in this study was also very low, between 10.2 and 30.4 per 10,000 dog years at risk, suggesting that TPLO, like fracture repair, is of minimal carcinogenic concern (4, 5).

What also remains unknown is whether the incidence of implant-associated tumors will increase with the increasing frequency of medical procedures incorporating implants, or potentially decrease because of improved quality and quantitative properties of the devices utilized and improved implantation techniques. Arthur *et al.*'s recent study showed an increasing incidence of OSA during the study period (1970-2000), but this observation may simply be a reflection of the significant advances in veterinary care, diagnostics and owner expectations during that time period (2).

The causal relationship between implants and sarcomas remains difficult to assess given the rarity of these tumors. Furthermore, there is nothing to distinguish them histologically from spontaneous OSAs (3). Anatomically, however, there are distinctions (2, 3, 4, 5, 7, 10). In contrast to spontaneously-arising OSA, which occurs most commonly in the metaphyseal region of the forelimbs, implant-

associated disease tends to occur in the diaphyseal region of the hindlimbs, most often the proximal tibia, i.e. the site of TPLO plate placement (2, 4, 5). In fact, in Sartor *et al.*'s study there were no cases of proximal tibial osteosarcoma except at a TPLO site (4). This anatomical association with previously placed metallic hardware was observed bilaterally in both cases.

Latency is also important in establishing the association between implant placement and tumor occurrence. Both Sartor *et al.* and Selmic *et al.* demonstrated that the younger the dog at the time of their orthopedic procedure, the more likely OSA was to develop (4, 5). The median latency period for implant-associated neoplasia in general is reported as approximately 5.5 years (3). The mean interval between fracture repair specifically and tumor diagnosis was previously reported as 3.5 years (range 2-8 years) (9) and 5.8 years (6), but more recently a more prolonged median latency period of 7.5 years (range: 3.7- 9.6 years) was reported (2). The median interval from TPLO to OSA specifically has been reported as 4.5 years (4) and 5.3 years (range 1-10.7 years) (5). In the cases presented here the latency periods were 7.5 years and 2.5 years respectively.

Before accepting OSA as implant-related, it is necessary to establish that the tumor conforms to the principles accepted for biomaterial-associated sarcomas, such that they develop in the vicinity of the biomaterial after an appropriate period of latency, and to exclude other factors known to cause sarcomas. Case 2 is interesting, as the right distal tarsal tumor is not immediately anatomically associated with the implant. It has, however, been suggested that some of the hypothesized carcinogenic factors of metallic implants have wider reaching impact on tumor microenvironment than simply in the immediate region.

Given the large number of dogs with metallic implants, the commonality of OSA, and the relative rarity of implant-associated OSA, it has been challenging to demonstrate a direct causal relationship between the two. Conversely, it is naïve to conclude that all implant-associated sarcomas are coincidental. If we accept that in rare cases this complication does occur, the question becomes what to do? Potential carcinogenesis is not a currently accepted reason to remove orthopedic hardware after fracture healing in people, nor a reason to discourage procedures such as hip arthroplasty, although caution is advocated by some surgeons in high risk patients (2). More research is required to elucidate the pathogenesis of implant-associated neoplasia in dogs and its clinical significance in the increasing population of dogs undergoing procedures incorporating metallic implants.

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