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Malignant Transformation to Chondroblastic Osteosarcoma Following Serratia liquefaciens-Induced Polyostotic Osteomyelitis in a German Shepherd Dog

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ABSTRACT

The emergence of bone neoplasms secondary to long-standing osteomyelitis is considered an uncommon and typically delayed outcome in both humans and veterinary patients. We report a case of malignant change—specifically a chondroblastic osteosarcoma—in a 7-year-old German shepherd previously affected by polyostotic osteomyelitis triggered by Serratia liquefaciens at 15 months of age. The neoplasm arose in the right humeral diaphysis, one of the earlier infection sites. To our knowledge, this represents the first documented canine case of polyostotic osteomyelitis linked to Serratia liquefaciens.

Keywords: Bone neoplasm, Chondroblastic osteosarcoma, Chronic bone infection, Serratia liquefaciens

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Introduction

Septic polyostotic osteomyelitis is an infrequent condition in dogs, characterized by multi-bone involvement and generally originating from long-standing bacterial or fungal infection [1–7]. Many organisms are capable of producing osteomyelitis, although bacteria are reported most often [8]. Despite this, fungal etiologies appear more common than bacterial ones in polyostotic variants [8]. Numerous studies identify Staphylococcus spp. as the leading cause in companion animals, with other Gram-positive microbes (e.g., Streptococcus) and Gram-negative pathogens such as E. coli, Pseudomonas, Proteus, Pasteurella multocida, and Klebsiella spp. also implicated [9,10]. More recently, anaerobes—including Propionibacterium acnes, Gemella morbillorum, Bacteroides and Fusobacterium species—have been detected [6]. A previous investigation examining aerobic bacteria responsible for post-traumatic infection reported osteomyelitis caused by Serratia liquefaciens [11], a facultatively anaerobic, Gram-negative member of the Yersiniaceae family. In humans, infections by Serratia spp. (notably S. marcescens, S. liquefaciens, S. plymuthica) are well documented among immunocompromised individuals, injection-drug users, and patients undergoing invasive procedures [12].

Aggressive polyostotic bone lesions generally have a limited differential list, including primary or metastatic tumors, infectious or sterile osteomyelitis, and immune-mediated etiologies. Distinguishing bone cancer from osteomyelitis may be challenging even with radiology, although neoplastic progression typically shows faster osseous changes [13]. Long-standing inflammation is known to encourage neoplastic transformation and facilitate

oncogenesis [14–18]. Although rare and usually delayed, malignant change secondary to chronic osteomyelitis can occur, but the underlying mechanisms remain poorly defined; persistent inflammatory stimulation is assumed to contribute substantially [19].

This paper details a case of septic polyostotic osteomyelitis caused by S. liquefaciens in a 15-month-old female German shepherd, later developing a chondroblastic osteosarcoma in the right humerus six years after the initial infection.

Case Presentation

A 15-month-old, intact female German shepherd was presented to the Teaching Hospital of the Department of Veterinary Medicine, University of Bari (THDVM), because of weight-bearing lameness in the left forelimb and generalized weakness. According to the owner, four months earlier, the dog had experienced epistaxis, lethargy, fever, and grade-II lameness in the left forelimb. Laboratory work showed mild leukopenia, normocytic hypochromic anemia, increased platelet size with macroplatelets, substantially elevated phosphorus levels, and a marked rise in C-reactive protein (CRP) (4.12 mg/dL, reference 0.01–0.45 mg/dL). Serum proteins revealed mild increases in α1 and α2 globulins and a monoclonal γ-globulin spike. Serology indicated positivity for Ehrlichia canis (1:320 by IFA) and negativity for Leishmania infantum (ELISA). Treatment with doxycycline (10 mg/kg PO SID for 21 days) resulted in seronegative status for Ehrlichia spp.

Due to progressive worsening of lameness, the dog was referred for further evaluation. On examination, body temperature was normal (38.7 °C). Pain was evident on deep palpation, accompanied by soft-tissue swelling over the left humerus and bilateral forelimb muscle atrophy. Updated bloodwork showed severe normocytic hypochromic anemia, lymphocytosis (3225/µL), eosinophilia (1032/µL), persistent elevation of CRP, and increased serum phosphorus.

Radiographs revealed multifocal osseous abnormalities compatible with polyostotic osteomyelitis, affecting the left and right humeral diaphyses, the left proximal tibial epiphysis, and ribs 5–7 bilaterally. Both humeri displayed periosteal proliferation, cortical thickening, exostoses, and bone sclerosis, with intermixed radiolucent regions indicating rarefaction. These findings were more severe on the left **(Figure 1a)** than the right **(Figure 1b)**.

Hind-limb radiographs showed no right-side lesions, but enlargement of the nutrient foramen in the left proximal tibia was noted. Thoracic projections (right and left laterals and dorsoventral) identified localized periosteal reactions on the right 5th–7th ribs and the left 6th rib **(Figure 2)**.

Initial treatment included amoxicillin/clavulanic acid (25 mg/kg PO BID for 3 weeks), carprofen (2 mg/kg PO BID), and pantoprazole (1 mg/kg PO SID for 10 days), resulting in visible clinical improvement.

After one month the dog returned with marked weakness and a draining fistula over the left humerus producing purulent material. Microbiological testing of blood and urine yielded negative results. Biopsies of lytic areas in both humeri showed nonspecific chronic inflammation. Bone marrow aspirates tested positive for Ehrlichia spp. via PCR. Fine-needle aspiration of the left suprascapular lymph node revealed septic pyogranulomatous inflammation, mild lymphoid hyperplasia, and atypical neutrophils.

Mycological and bacterial cultures from bone biopsy samples identified S. liquefaciens, sensitive to amikacin, ceftazidime, enrofloxacin, and ciprofloxacin. Treatment was initiated with enrofloxacin (5 mg/kg PO BID for 60 days), doxycycline (10 mg/kg PO SID for 42 days), gabapentin (10 mg/kg PO SID for 30 days), meloxicam (0.1 mg/kg PO SID), and omeprazole (1 mg/kg PO SID for 10 days).

After 60 days, the dog returned in excellent condition with resolved lameness. Blood parameters and biochemistry values had normalized. Bone marrow PCR confirmed Ehrlichia negativity, and radiographs showed substantial bone remodeling.

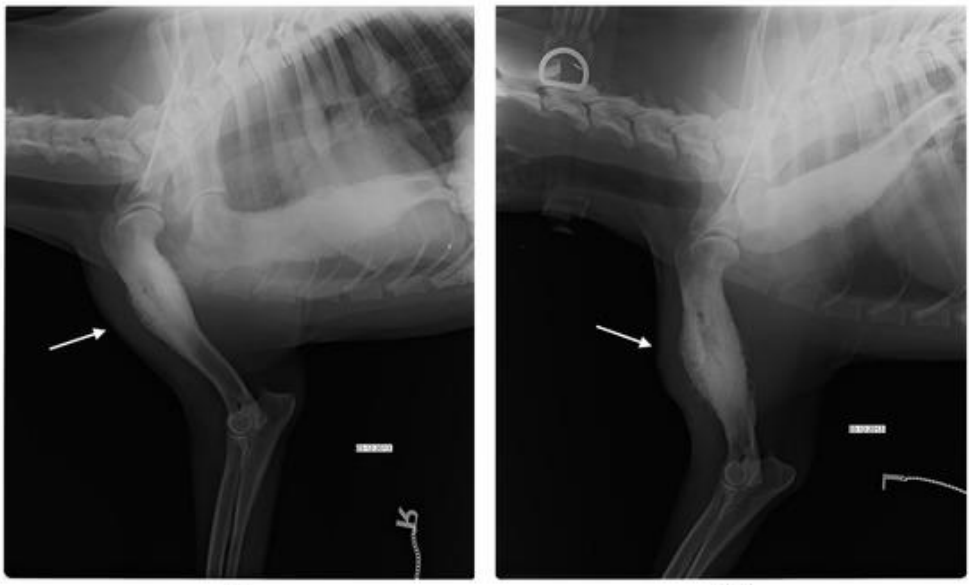

Figure 1. Mediolateral (ML) projections of the left (a) and right (b) humeri at the initial presentation demonstrate widespread sclerosis and periosteal proliferation along the diaphysis (white arrow).

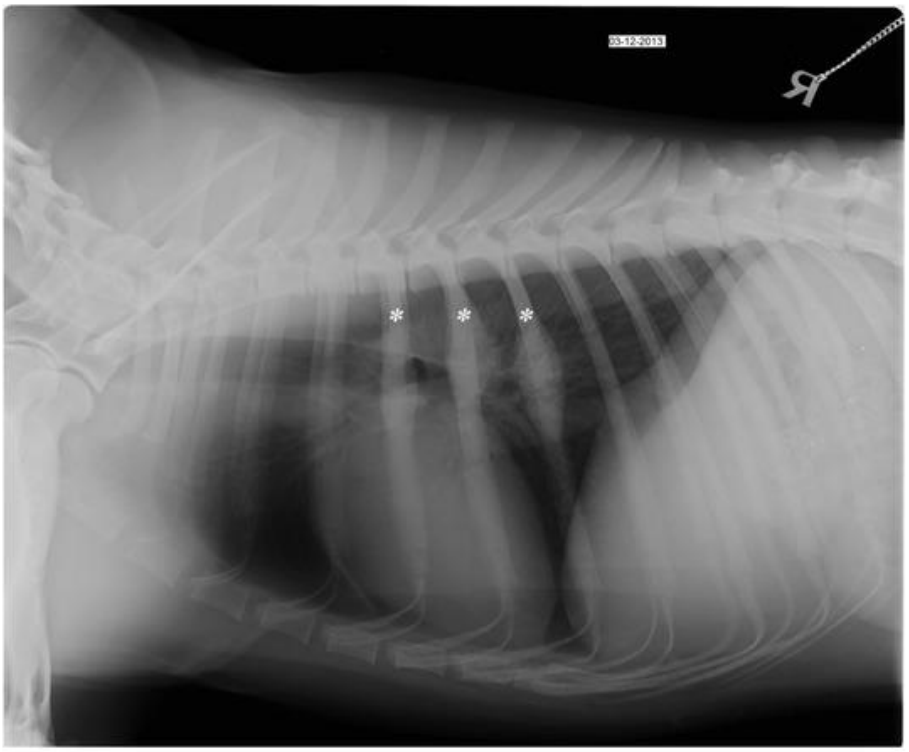

Figure 2. Right lateral (LL) thoracic radiograph from the first visit reveals localized periosteal new bone on ribs 5, 6, and 7 (asterisk)

After 6 years, the dog was brought back to the THDVM due to a 2-week progression of grade-III lameness in the right forelimb. On examination, marked muscle wasting of the abductor region and pronounced pain on manipulation of the right limb were evident, whereas the left limb was unremarkable. Radiographs (mediolateral and craniocaudal views) of the right humeral shaft disclosed combined lytic and sclerotic areas, an indistinct transition between abnormal and normal bone, severe cortical destruction, irregular periosteal proliferation, and extensive suspected neoplastic bone formation in adjacent soft tissues **(Figure 3a,b)**. These findings supported a presumptive diagnosis of a primary bone tumor.

A full-body CT scan was completed to assess the extent of disease. The right humerus exhibited substantial cortical loss, disorganized periosteal reaction with transitional zones, and patchy hyperdense foci in the medullary

cavity—changes compatible with a humeral neoplasm **(Figure 4a)**. CT evaluation of the left humerus showed cortical osteolysis with smooth, solid periosteal thickening, consistent with chronic osteomyelitis. Additionally, the mid-sections of the right 5th, 6th, 7th ribs and the left 6th rib displayed focal areas of cortical thickening indicative of hyperostosis **(Figure 4b)**.

Bone samples obtained during CT—taken from the right humeral mass and the osteolytic region of the left humerus—revealed chronic lymphoplasmacytic osteomyelitis with bone remodeling; no neoplastic cells or pathogens were detected, and blood cultures were negative. After 6 weeks of treatment with NSAIDs, gabapentin, and pamidronate disodium without clinical improvement and with worsening lameness, limb amputation of the right forelimb was elected.

Histopathological review of the entire excised bone confirmed a productive chondroblastic osteosarcoma (OSA) of the distal right humerus with extension into nearby soft tissues. Microscopically, the sample consisted of lamellar bone interspersed with irregular osteoid islands, bordered by malignant spindle-to-polygonal cells, arranged in sheets or short bundles with minimal vascular stroma and abundant extracellular osteoid. Multifocal areas of chondroid differentiation and extensive necrosis were present.

The owners declined conventional adjuvant chemotherapy using carboplatin or doxorubicin. Instead, the dog received a metronomic protocol with cyclophosphamide (15 mg/m² SID), firocoxib (5 mg/kg SID), and thalidomide (10 mg/kg PO SID). After 8 months, restaging CT identified metastatic spread to the vertebrae and thorax, and the dog was euthanized according to the owner's decision.

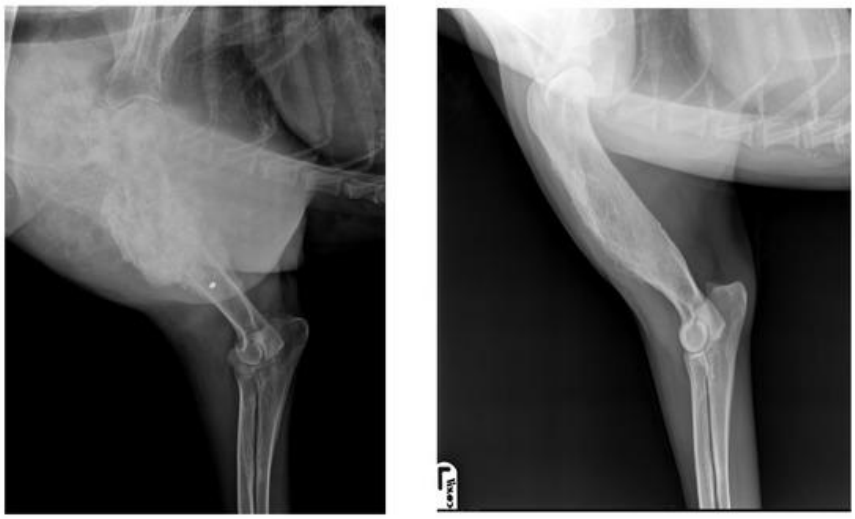

Figure 3. (a) Lateral radiograph of the right humerus, six years after the initial assessment, showing a heterogeneous proximal diaphyseal lesion with mixed lysis and sclerosis, an active irregular periosteal response, and a poorly distinguishable proximal transition between healthy and abnormal bone (asterisk) (b) Lateral radiograph of the left humerus, six years after the first visit, indicating residual periosteal thickening along the diaphysis

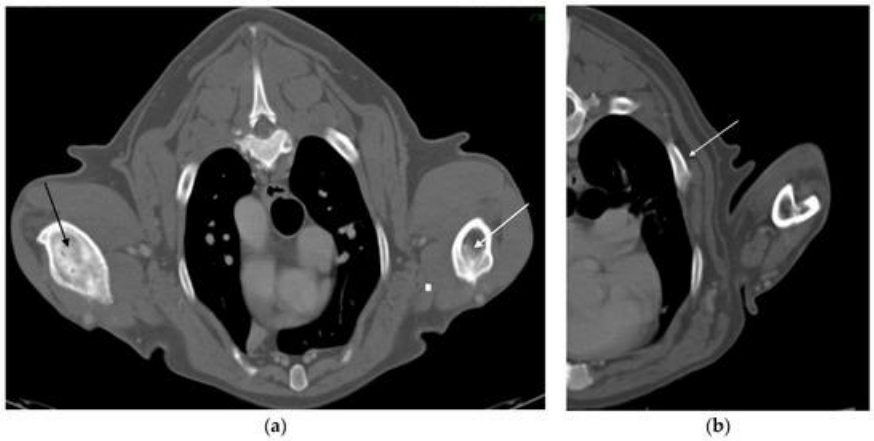

Figure 4. (a) Transverse CT image, six years after first presentation, depicting marked lysis of the right humeral diaphysis (black arrow). The contralateral humerus displays chronic osteomyelitis sequelae with

pronounced cortical thickening (white arrow). (b) Thoracic transverse CT reconstruction demonstrating focal rib hyperostosis (white arrow)

Discussion

This case outlines bone involvement by S. liquefaciens producing polyostotic osteomyelitis in a dog concurrently affected by Ehrlichia canis. Prior investigations indicate that Ehrlichia-associated immunosuppression can heighten vulnerability to additional pathogens, including bacteria, viruses, and protozoa [20], implying that prolonged infection and continuous immune activation may play a role in the onset of septic osteomyelitis. In this patient, the initial treatment for E. canis was shorter than recommended, allowing persistent systemic infection.
A unique aspect of this case is the recovery of S. liquefaciens, as this organism has not previously been linked to polyostotic osteomyelitis. The biofilm-forming capacity of S. liquefaciens likely provided protection from both humoral and cellular immune defenses, which were already compromised by ehrlichiosis [21]. Reports of this bacterium in dogs are rare, mainly involving intravenous catheter infections in parvoviral cases without subsequent bone involvement [22], and a post-traumatic infection identified before and after fracture stabilization [11].
In people, Serratia infections were not widely acknowledged until the latter half of the 20th century, with S. marcescens being the most frequently encountered species in clinical cases [23].
In this report, the identification of polyostotic osteomyelitis associated with Serratia was unusual [2-7], especially considering that most published cases involve monostotic forms [24]. The initial treatment with amoxicillin/clavulanic acid was not directed at the actual pathogen and therefore did not resolve the infection. Culturing bone biopsy samples was essential for determining the causative agent, as the resulting antibiogram made it possible to select an appropriate antimicrobial protocol. The combined administration of NSAIDs, pain-control medications, and targeted antibiotics reduced discomfort and soft-tissue inflammation. Given the predisposing factors and the dog's longstanding forelimb osteomyelitis, susceptibility to developing OSA was high [25], particularly since this tumor is common in large and giant breeds such as German shepherds [26]. Although the origin of OSA in dogs remains unclear, even mild trauma to skeletal tissue may initiate tumorigenesis [27], and chronic inflammation in general is known to support oncogenic processes [28-30].
Physical, chemical, or infectious insults initiate an inflammatory cascade which, if persistent, can disrupt local immune regulation, alter the microenvironment, and affect genes involved in cancer development [16]. If osteomyelitis is inadequately treated or left unresolved, the result is a chronic, resistant bone infection in which continuous inflammation leads to tissue destruction and may contribute to malignant change [16]. In humans, the interval between initial bone infection and eventual malignant transformation can span many years, commonly 18–72 years. In the present case, the progression from osteomyelitis to osteosarcoma occurred over 6 years. Standard management for localized OSA—amputation of the diseased limb combined with adjunct chemotherapy—typically provides good recovery, with a median DFI of 327 days and an MST of 383 days [26]. The owners declined conventional chemotherapy following amputation and opted for a metronomic regimen instead. Despite chronic lymphoplasmacytic osteomyelitis in both humeri, neoplastic transformation occurred only in one segment, though the appearance of additional tumors in other previously affected sites cannot be ruled out.

Conclusions

Serratia liquefaciens was isolated here for the first time from a bone specimen of a dog presenting with polyostotic osteomyelitis. This condition may pose a serious clinical challenge, and without timely treatment, can be life-threatening. Successful management depends on completing the full diagnostic work-up, including histopathological evaluation of bone biopsy samples. Chronic osteomyelitis may reappear intermittently, with remission periods of unpredictable length. Even after seemingly effective therapy, relapse rates remain high. Long-term control of chronic osteomyelitis is complex and requires coordinated input from radiologists, microbiologists, and surgeons. Despite extensive antibiotic courses and surgical intervention, flare-ups can persist for many years, and complete resolution cannot be confidently assured. In cases of aggressive osteomyelitis, particularly in medium to large breeds, extended monitoring is recommended due to the potential for delayed tumor formation.

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