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*Corresponding author

Daniel J Duffy, Diplomate ACVS-S, Diplomate ECVS, Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, 1052 William Moore Drive, Raleigh, NC, 27607, USA

Keywords

Hyperesthesia; Dogs; Normochromic Anemia; Arthrocentesis; Neutrophilic Inflammation

Abbreviations

CRMO: Chronic Recurrent Multifocal Osteomyelitis; GMS: Grocott's Methenamine Silver; CRI: Continuous Rate Infusion

Case Report

A Clinical Case of Chronic Recurrent Multifocal Osteomyelitis in a Dog

Duffy DJ[1*], Kendall AR[1] and Ramos-Vara JA[2]

[1]*Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, USA*

[2]*Comparative Pathobiology (Ramos-Vara), College of Veterinary Medicine, Purdue University, USA*

Abstract

A 5-year-old 5.5-kg castrated male Italian Greyhound was evaluated for bone pain, generalized hyperesthesia and fever. Physical and orthopedic examination revealed non-specific bone pain and hyperesthesia; radiographs were then performed. Radiological findings included smooth to irregular periosteal reaction on the caudal, lateral and medial aspect of the proximal right humeral diaphysis. Moth-eaten to permeative lysis was present on the humeral head and metaphysis with mild associated sclerosis. Because the dog's clinical signs worsened despite instituted medical management, synovial fluid samples were obtained and submitted for cytological analysis and culture. Surgical biopsy specimens were obtained from the right proximolateral diaphysis of the right humerus. Results of histochemical analysis, cytology and culture of bony tissue and blood were negative for bacterial or fungal agents. These clinical, imaging, and histopathologic findings were compatible with Chronic Recurrent Multifocal Osteomyelitis (CRMO). To the author's knowledge, this is the first report of chronic recurrent multifocal osteomyelitits in a dog. CRMO should be considered as a differential diagnosis in dogs with signs of bone pain with or without fever. Further investigation into therapeutic treatments and causative etiologies in veterinary patients is warranted.

Case Report

A 5-year-old 5.5-kg (12.1Kg) castrated male Italian Greyhound was presented for a progressive history of waxing and waning generalized pain, hyperesthesia, hyporexia and fever ranging from 102.9 – 103.6 °F that was documented on serial examinations that had become acutely worse in the last 2 months. Blood work obtained by the referring veterinarian prior to presentation showed evidence of mild hypophosphatemia (2.3 mEq/L; reference range, 2.5 to 6.0 mEq/L), a mature neutrophilia (11,550 /uL; reference range, 2060 to 10,600/uL) and monocytosis (1650 /uL; reference range, 0 to 840 /uL). No improvement was appreciable with supportive care consisting of Carprofen 2.2 mg/kg BID PO, Enrofloxacin 5 mg/kg BID PO, Tramadol 5 mg/kg TID PO, Metoclopramide 0.2 mg/kg TID PO and a dietary change to a proprietary brand gastrointestinal diet as the referring veterinarian suspected a diagnosis of pancreatitis. A month after the onset of worsening signs, the patient was re-assessed by a different veterinarian who localized pain upon manual cervical palpation to C1-C3 and the thoracolumbar spine. At this time, the dog was prescribed Prednisone (Predinsone, West-ward Pharmaceutical Corp, Eatontown, NJ) at a tapering dose (0.5-0.1 mg/kg BID PO q2 weeks) and started to receive acupuncture treatments twice weekly for one month. There was evidence of a marked initial improvement after initiation of steroidal therapy, however recurrence of hyperesthesia was seen upon tapering of the medications that became acutely worse after discontinuation. At this time the dog became acutely anorexic. He then presented to the Internal medicine service at Purdue University College of Veterinary Medicine for non-relenting pain and hyporexia. Upon initial examination, physical exam findings revealed a fever of 105.1 °F, heart rate of 120 bpm and a respiratory rate of 18 bpm. Generalized pain was appreciable upon orthopedic examination with a stiff and stilted gait that did not localize lameness to a single limb. Pain was elicited upon maximal extension and flexion of the right scapulohumeral joint, coxofemoral joints and stifles bilaterally and mild effusion was noted upon palpation of the left antebrachiocarpal joint. Neurological examination was unremarkable; however, there was moderate pain on spinal palpation localized to the thoracolumbar junction. A complete blood count, serum biochemistry profile, and urinalysis were performed. Abnormalities included evidence of a normocytic, normochromic anemia (35.6%, 67.9 MCV fL, 32.3 MCHC g/DL reference range 37 to 55, MCV 60-75, MCHC 32-36), hyperproteinemia (8.4 g/dL; reference range, 6.0 to 8.0 mg/dL), leukocytosis characterized by a neutrophilia with a left shift (30.7 K/uL; reference range, 3 to 12 K/uL, band neutrophils 0.33 K/uL; reference range, 0 to 0.3 K/uL) and a monocytosis (1.65 K/uL; reference range, 0.15 to 1.35 K/uL). There was evidence of a mild azotemia, with elevated BUN (76 mg/DL; reference, 7 to 32 mg/dL) and elevations in serum creatinine (1.6 mg/dL; reference range, 0.5 to 1.5 mg/dL), hypocalcemia (9.4 mg/dL; reference range, 9.7-12.3 mg/dL), elevated alkaline phosphatase (299 IU/L; reference range, 20 to 157 IU/L) and hypercholesterolemia (468 mg/dL; reference range, 125 to 301 mg/DL). A commercially available snap test (4DX Snap Test - SNAP 4Dx Plus Test Kit, IDEXX Laboratories, Westbrook, Me) was negative for *Anaplasma phagocytophilum*, *Anaplasma platys*, *Borrelia burgdorferi*, *Dirofilaria immitis*, *Erlichia canis* and *Erlichia ewingii*. Fluid therapy was initiated with a balanced crystalloid solution (Plasmalyte-A, Baxter Healthcare Corp, Deerfield, Ill) (25 ml/hr, 60 ml/kg/day plus 5% dehydration corrected over 24 hours, IV) and Continuous Rate Infusion (CRI) of fentanyl (Fentanyl citrate injection USP, Hospira Inc, Lake Forest, Ill) (4 mcg/kg/hr, IV, CRI) and lidocaine (Lidocaine HCL 2%, VEDCO, St Joseph, Mo) (20 mcg/kg/min, IV, CRI) for analgesic therapy. Orthogonal radiographic views of the thorax and abdomen were performed. Thoracic radiographs revealed a smoothly marginated area of periosteal proliferation along the right caudo-proximal humeral cortex with concurrent mixed permeative lysis and sclerosis present within the head and proximal diaphysis of the right humerus. Irregular periosteal proliferation, mixed permeative lysis and sclerosis was identified along the ventral aspect of the vertebral body of T13 and the cranio-ventral aspect of the vertebral body of L1 correlating with the site of pain on palpation (Figure 1). Cardiovascular and pulmonary structures were within normal limits. Abdominal radiographs revealed similar bony changes, as noted in T13 and L1, within the vertebral body of L4 and a low body condition score. The bony changes appreciable on thoracic radiographs prompted further focused radiographic evaluation of the right humerus. There was evidence of smooth to irregular periosteal reaction on the caudal, lateral and medial aspect of the proximal right humeral diaphysis. There was also moth-eaten to permeative lysis present on the humeral head and metaphysis with mild associated sclerosis. The transitional zone between normal and abnormal bone was long and ill-defined (Figure 2).

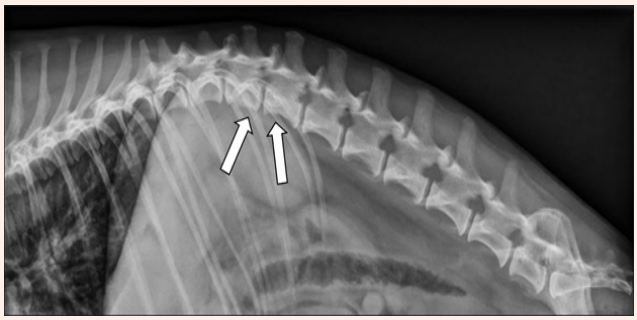

Figure 1: Left lateral radiographic projection of the thoracic and lumbar spine. Irregular periosteal proliferation, mixed permeative lysis and sclerosis can be identified along the ventral aspect of the vertebral body of T13 and the cranio-ventral aspect of the vertebral body of L1 (demonstrated by the white arrows).

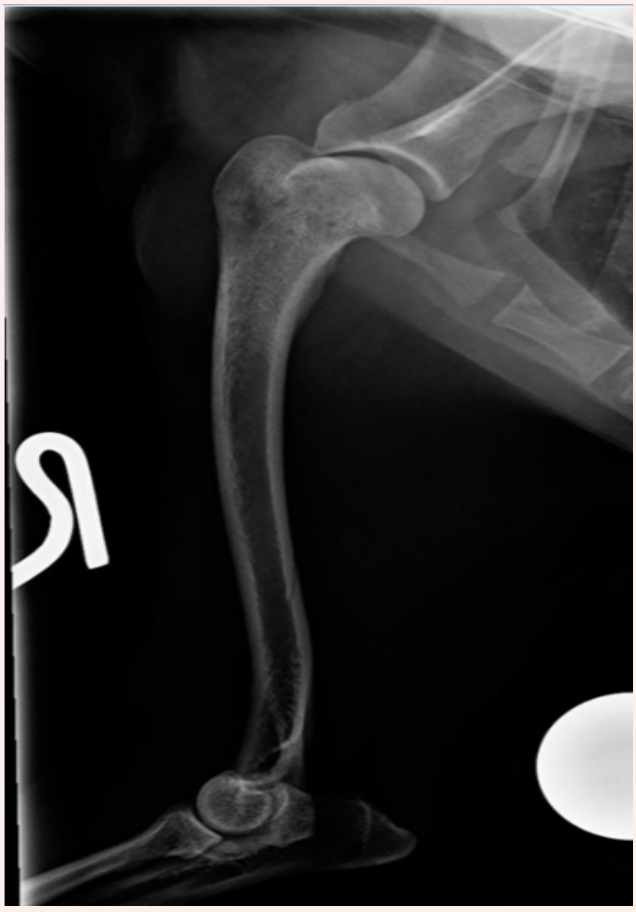

Figure 2: Lateral radiograph of the right humerus. Smooth to irregular periosteal reaction on the caudal, lateral and medial aspect of the proximal humeral diaphysis. There is also moth-eaten to permeative lysis appreciated on the humeral head and metaphysis with mild sclerosis.

The following day the dog received premedication with Fentanyl (3 mcg/kg, SQ) and anesthesia was induced with intravenous Propofol (Propofol, Propoflo28, Abbott Laboratories, North Chicago, Ill) (4-6 mg/kg, IV) titrated to effect. The dog was intubated with a size 6.5 endotracheal tube and was maintained on Isoflourane (Isoflurane USP, Halocarbon Products Corp, River Edge, Nj) and oxygen while arthrocentesis, fine needle aspiration of the affected lesion and bone biopsy of the right proximal humerus were performed. Synovial fluid samples obtained from the left carpus and both stifles were submitted for cytological analysis and microbial culture. Surgical biopsy specimens were obtained from the right proximolateral diaphysis/metaphysis of the right humerus with a 5-mm Michelle trephine (Michelle trephine, Sontec Instruments, Englewood, Colo). Biopsy specimens were first used for direct impression smears by roll preparation prior to fixation in neutral-buffered 10% formalin solution and tissue was concurrently submitted for bacterial and fungal culture. Blood was also obtained for culture. The dog recovered uneventfully from anesthesia however hematochezia was seen following the procedure. The dog continued to show evidence of marked pain and treatment with Gabapentin (Gabapentin, United States Pharmacopeia, Rockville, Md) (4.7 mg/kg, PO, TID), Pantoprazole (Pantoprazole, Protonix, Wyeth Pharmaceuticals Inc, Philadelphia, Pa) (1 mg/kg, IV, SID) and Metronidazole (Metronidazole oral suspension (62.5 mg/mL), PCCA, Houston, Tex) (10 mg/kg, PO, TID) was instituted. The following day the dog was administered Pamidronate (Aredia, Novartis Animal Health US Inc, Greensboro, NC) (1 mg/kg, IV, 5 mg/1.76 ml in 250ml of 0.9% NaCl slowly over 7 hours). Following the infusion, the dog appeared to be more painful and was administered Dexamethasone SP (Dexmethasone Dexaject SP 4 mg/mL injection, Bimeda-MTC Animal Health Inc, Oakbrook Terrace, Ill) (0.067 mg/kg, IV, SID). The dog showed significant clinical improvement and was discharged pending histopathological analysis with specific staining and culture of tissue and blood. The dog was discharged with Gabapentin (4.7 mg/kg, PO, TID), Prednisone (0.5 mg/kg, PO, SID), Buperonorphine (Buprenorphine 0.3 mg/mL, Hospira, Lake Forest, Ill) (0.01 mg/kg, PO, TID), Metronidazole (10 mg/kg, PO, TID) and Ranitidine (Zantac, Glaxo Wellcome, Research Triangle Park, NC) (2 mg/kg, PO, TID). The expectation was to taper and then discontinue steroidal therapy and initiate Non-Steroidal Anti-Inflammatory (NSAID) therapy.

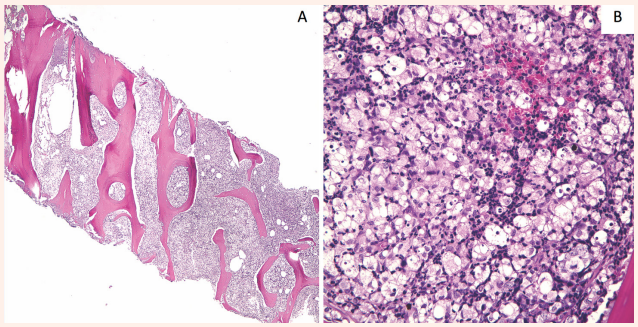

Figure 3: Histological image from a core biopsy obtained from the right proximal humerus. (A) There is increased cellularity within the marrow cavity. Hematoxylin-eosin stain. 4X (B) Detail of the inflammatory infiltrate consisting mostly of neutrophils and foamy macrophages. Hematoxylin-eosin stain. 40X..

After specimen collection for histopathology, samples were decalcified, processed, embedded in paraffin, and sectioned at a thickness of 5µm. Tissues were stained with hematoxylin-eosin, Giemsa, acid-fast, and Grocott's Methenamine Silver (GMS) stains and examined by use of light microscopy. The bone core biopsy examined consisted of trabecular bone. The marrow was hypercellular and partially filled with numerous hypersegmented neutrophils and foamy macrophages. Some areas contained increased numbers of segmented neutrophils. Few hematopoietic cells including megakaryocytes were observed. Osteoblastic or osteoclastic activity was not observed in any sample. A neutrophilic infiltrate was also present in the peri-osseous soft tissue. (Figure 3) The adjacent skeletal muscle was partially replaced by connective tissue. Histochemical stains (Giemsa, acid fast stain and GMS) did not reveal microorganisms. Results of aerobic and anaerobic bacteriologic cultures and fungal culture of each of the biopsy tissue specimens removed from the proximal humeral lesion were negative for microorganisms. Blood cultures were also negative, with no growth after enrichment. Testing specific for Bartonella spp. was also negative. Cytological roll preparations were moderately to highly cellular, consisting of a heterogeneous cell population with few keratin bars, squamous epithelial cells, few lysed nuclei, minimal nuclear streaming, and a few blue cytoplasmic fragments and pink proteinaceous material in the background. The predominant cells were of hematopoietic origin alongside mixed inflammatory cells. The hematopoietic cells consisted of early and late myeloid and erythroid precursors. Early lymphoid precursors were also present. Increased numbers of non-degenerate neutrophils and few small lymphocytes and rare eosinophils were seen, as were small aggregates and individually scattered plasma cells. Increased numbers of macrophages (activated and epitheloid) were also present, exhibiting occasional multinucleation (up to three nuclei) and leukophagia. These were sometimes intermixed with plump spindle cells

(fibroblasts). No infectious agents were observed in any slide. Histochemical staining with GMS, Giemsa and Fite's stains did not reveal any infectious agents. Aspirates of the right stifle revealed moderate neutrophilic inflammation, the left stifle showed evidence of moderate mononuclear inflammation and mild neutrophilic infiltrate, and the left carpus revealed no cytological abnormalities with no microscopic etiologic agents seen in any of the slides upon review by a board-certified pathologist. A presumptive diagnosis of Chronic Recurrent Multifocal Osteomyelitis (CRMO) was made based on exclusion of other causes after diagnostic testing and the dog's clinical history.

The dog's clinical signs improved initially however continued to worsen following diagnosis despite instituted treatment, and further treatment and diagnostics within the hospital were declined. Due to perceived poor quality of life by the owners, they elected for humane euthanasia. A necropsy examination was offered but declined by the client.

Discussion

Chronic Recurrent Multifocal Osteomyelitis (CRMO) is an extremely rare clinical disease diagnosed in paediatric and adolescent human patients. It was first described by Giedion et al. in 1972 [1] with only individual case reports and small case series reported within the human literature to date [1-9]. There is also an isolated case of CRMO described in a lemur with a similar clinical presentation and near identical histological findings [10]. To the authors knowledge, this is the first canine case of CRMO that has been described within the veterinary literature. Due to the rarity of the disease, there is a paucity of information and to date no published epidemiological data is available; however, current incidence was posed to be 1:1,000,000 according to one human study [11]. CRMO has appeared within the human literature under many differing titles; including subacute symmetric osteomyelitis, tumoral osteomyelitis, chronic symmetric osteomyelitis, pyogranulomatous osteomyelitis, chronic multifocal cleidometaphyseal osteomyelitis, chronic multifocal symmetric osteomyelitis and sterile osteomyelitis [2,6,8,9,12,13]. The disease manifests as recurrent flares of inflammatory bone pain related to the presence of multiple foci of sterile osteomyelitis the cause of which is unknown with similar signs of waxing and waning periodic lameness as was evident in this case [14]. A clinical spectrum of signs are appreciable; however, active lesions are typically characterized by warmth, tenderness, localized bony swelling, progressive and sometimes intermittent pain with or without fever [7,11,14]. In human patients predilection sites for CRMO exist, with lesions most commonly affecting the tibia, femur, pelvis and clavicle. Other osseous sites such as vertebrae have been described in 4-30% of cases, as was seen in this Italian Greyhound [7,14]. CRMO has no identifiable bacterial, fungal or neoplastic involvement and lesions are sterile (aseptic) in nature. Ruling out infectious aetiologies is of primary importance to obtain a diagnosis by exclusion [14]. To distinguish CRMO from neoplastic or infectious causes of osteolyelitis, bone biopsy with histopathologic examination, special staining of histopathologic samples and culture of affected tissue is typically warranted. In human patients, prophylactic trial treatment with antibiotic therapy is commonly performed and whole-body imaging with Magnetic Resonance Imagining (MRI) and radionucleotide bone scanning are often used to identify asymptomatic foci where there is evidence of radiopharmaceutical uptake [14,15]. CRMO bony lesions generate hypointensity on T1 images and hyperintensity on T2 images [16]. A recent human MRI imaging study revealed that metaphyseal lesions were accompanied with epiphyseal lesions in 67% of cases [16,17].

Radiography is commonly the first-line imaging modality utilised due to its low cost, superior spatial resolution and availability when evaluating bony pathology; however, radiographically apparent lesions may not be seen initially with CRMO [14]. In human patients, lesions resemble those of acute osteomyelitis and are usually localised to the metaphyseal or physeal region of the bone as was present in the above case [9,18]. Involvement of the diaphysis has also been described [19]. As the disease progresses; osteolytic, sclerotic, periosteal proliferation or mixed bony changes may be seen however a wide variety of radiographic signs have been reported [9]. In the canine patient presented here, irregular periosteal proliferation with mixed permeative lysis and sclerosis were identical to the bony changes seen radiographically in chronically affected human patients with CRMO [9,18]. Differential diagnoses that should be considered in such cases include but are not limited to; osteomyelitis, primary bony neoplasia (osteosarcoma, fibrosarcoma, lymphoma, histiocytosis) and fungal disease. Diaphyseal lesions with CRMO, as seen in the present case, have been reported visible only as cortical thickening in people [19]. Bone-biopsy from CRMO lesions are consistent with non-specific osteitis [14,20]. Morphologically CRMO begins as an acute inflammatory process with a predominance of polymorphonuclear leucocytes, with occasional osteoclastic bone resorption and areas of osteolysis. Abscess formation may also be a histologically evident finding. As CRMO becomes more chronic, the predominant histopathologic features are reactive bone formation, bone sclerosis and a predominantly lymphocytic and inflammatory infiltrate is seen with surrounding fibrosis [20]. The presence of microorganisms or infectious agents are not typically identified, even with the recruitment of special staining techniques and culturing of tissue for microbial involvement as was evident in this canine patient.

The pathophysiology of the disease remains elusive in human patients [14], however association with Crohn's disease [7], pyoderma gangrenosum [2], and viral disease have all been suggested as potential eitiologies [12]. Significant association has been made with multi-factorial immune mediated and autoinflammatory diseases [14], and histological findings support this theory [20]. Recently, it has been suggested that CRMO may represent a pediatric form of SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) and is largely considered to be auto-inflammatory in nature [21]. In the human literature, there are reports of families with two affected offspring being born to unaffected biological parents, suggesting a genetic contribution and an autosomal recessive mode of inheritance [22]. Although no randomized controlled trials are available, general consensus exists in regard to treatment of CRMO in human patients. Treatment with NSAIDs have been shown to be effective in some cases in mediation of bone pain supported by the use in five diagnosed patients with CRMO that all underwent progressive clinical improvement (mean, 2.8 months), with no apparent radiological lesions after a mean period of 10.5 months [23]. In the current case, NSAID therapy was not initiated due to the positive clinical response seen with steroidal therapy and the fact that washout treatment would have been necessary prior to NSAID implementation. In cases refractory to NSAIDs, systemic immunosuppressive therapy with glucocorticoids, bisphosphonates and TNFa antagonists are commonly employed. Oral glucocorticoids are generally highly effective in the majority of human cases [14], as was seen in the patient presented here, however they are generally not utilized due to their significant adverse side effects appreciable with long-term treatment. A small case series reported complete resolution of clinical and MRI documented bony lesions with the use of pamidronate in nine pediatric patients with CRMO [24], however there is limited information regarding dosage, dose interval at which beneficial effects are appreciable and duration of pharmacologic administration. TNFa antagonists have shown resolution in clinical cases unresponsive to other utilised therapies [7,14].

The authors strongly believe that the diagnosis of CRMO is warranted on the basis of similarities with both clinical, radiological and histopathological abnormalities seen in humans. To the authors' knowledge, this is the first canine case of CRMO that has been identified and reported within the veterinary literature. This case shows many similarities to those described in the case of a lemur diagnosed with suspect CRMO and people [10,11,14,19,20]. Unlike is often demonstrated in human patients, dramatic improvement was seen with the use of systemic glucocorticoid therapy at initial immunosuppressive doses. Further exploration and use of bisphosphonates is warranted after diagnosis of CRMO in clinically affected patients. CRMO should be considered as a differential diagnosis in dogs presenting with bone pain and supporting radiographic lesions after ruling out infectious eitiologic agents.

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