Imaging features of chronic recurrent multifocal osteomyelitis (CRMO) involving the vertebral column of a lemur with subsequent paraplegia due to pathological fractures

Beeldvormingskarakteristieken van chronisch recidiverende multifocale osteomyelitis van de wervelkolom van een lemur resulterend in paraplegie ten gevolge van pathologische fracturen

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ABSTRACT

A seven-year-old, female ring-tailed lemur was referred for progressive non-ambulatory paraplegia. A computed tomographic (CT) scan of the whole body revealed multifocal lytic lesions involving multiple vertebrae and several pathological vertebral fractures. Necropsy and histopathology identified pyogranulomatous osteomyelitis. The imaging and histopathological findings resemble chronic recurrent multifocal osteomyelitis described in human medicine.

SAMENVATTING

Een zeven jaar oude, vrouwelijke ringstaartmaki werd doorverwezen vanwege een voorgeschiedenis van progressieve non-ambulatoire paraplegie. Een computertomografische scan (CT) van het volledige lichaam toonde multifocale osteolyse van meerdere wervels en meerdere pathologische wervelfracturen. Autopsie en histopathologisch onderzoek toonden pyogranulomateuze osteomyelitis aan. De bevindingen van beeldvorming en histopathologie zijn gelijkaardig aan chronisch recidiverende multifocale osteomyelitis zoals beschreven in de humane geneeskunde.

INTRODUCTION

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare pathology of unknown etiology primarily affecting children and adolescents; however adult onset disease has also been described (Sato et al., 2017; Girschick et al., 2018; Mahady and Ladani, 2019). It mainly affects the clavicles, and metaphysis of long bones, the vertebral bodies are uncommonly affected. Characteristic imaging findings resemble those of osteomyelitis mainly including osteolytic lesions, often with a sclerotic margin (Baulot et al. 1998; Panwar 2016). The diagnosis is made by exclusion, combining imaging, histopathology, and absence of infectious agents (Panwar, 2016). The pathology has been reported once in a lemur. In that case, the long bones were affected. To the best of the authors' knowledge, this is the first case describing vertebral body involvement of CRMO in a lemur. Additionally, the case was complicated by the presence of multiple pathological fractures, which is similar to a case report in human medicine from 1998 (Baulot et al., 1998).

CASE DESCRIPTION

A seven-year-old, female ring-tailed lemur (*Lemur catta)* from a wildlife park in Belgium, was presented to the Medical Imaging Department of Ghent Uni-

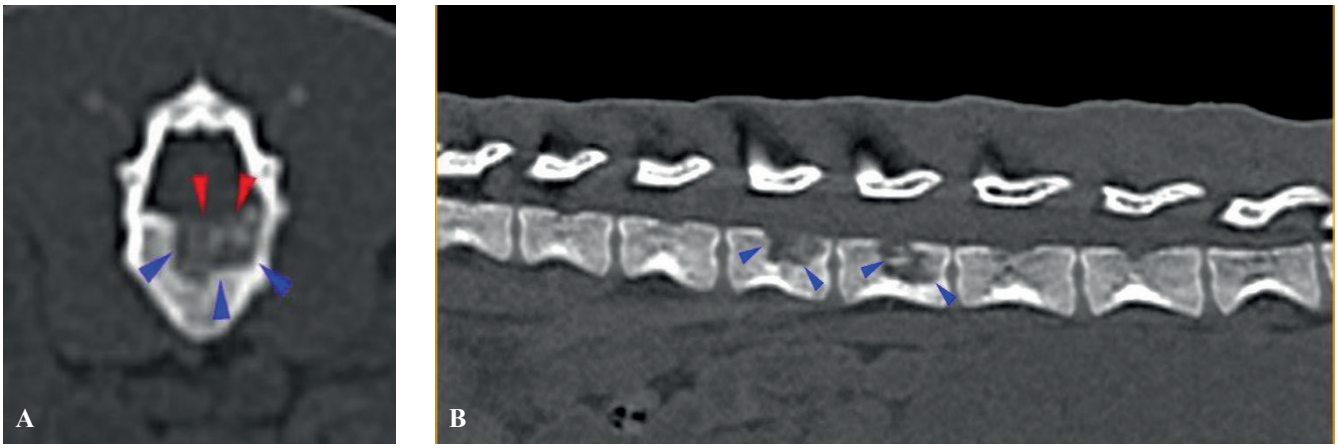

Figure 1. A. Transverse image at the level of L3 and B. Sagittal reconstruction of the lumbar vertebral column showing osteolytic lesions (blue arrowheads) with thinning of the overlying cortex (red arrowhead).

versity for further diagnostics due to non-ambulatory paraplegia. One-and-a-half months prior to presentation, it had been noticed that the lemur stayed more on the ground, avoided climbing the enrichment apparatus and additionally started eating sand litter from the ground. Three weeks later, she was seen by the local emergency department due to intestinal mechanical ileus and underwent abdominal surgery to correct the sand impaction. Abdominal x-rays done at that time did not show any skeletal changes in the included caudal thoracic and lumbar vertebral column, although imaging was not specifically focused on the vertebral column. At the time of surgery, biochemistry and hematology results were within reference range and clinical examination was normal except for a tense abdomen. She recovered uneventfully from the surgery but the reluctance to jump and climb persisted. Neurological examination demonstrated hind-limb ataxia with normal spinal reflexes and intact deep-pain sensation. Differential diagnosis included possible trauma, infectious causes or neoplasia. A treatment decision was made ten days after the abdominal surgery to start with glycocorticosteroid therapy (prednisolone 1 mg/kg BID) and antibiotics (clindamycin 11mg/kg SID) with initial good response to the treatment. However, on the 10th day following treatment initiation, acute worsening with non-ambulatory paraplegia, spinal hyperesthesia, diminished spinal reflexes with intact deep pain sensation was recorded. The lemur was referred for further diagnostics to the Medical Imaging Department of the Faculty of Veterinary Medicine (Ghent University).

The lemur was sedated with intramuscular injection of medetomidine (0.04 mg/kg) and ketamine (5mg/kg). The general anesthesia was maintained with isoflurane after induction and intubation.

A CT (Toshiba Aquillon ONE TSX-301C) study of the whole body of the lemur was performed, which showed multifocal geographic to permeative lucent regions involving multiple vertebral bodies of the thoracolumbar spine with most severe changes noted at the vertebral bodies of the 5th, 6th and 11th thoracic vertebrae (T5, T6, T11) and 2nd, 3rd and 4th lumbar vertebrae (L2, L3 and L4) (Figures 1A and 1B). Additionally, acute to subacute pathological fractures with foreshortened, partially collapsed vertebral bodies were affecting T5, T6 and T11 with displacement of fracture fragments into the vertebral canal at the level of T5, causing severe compression on the dural sac (Figures 2A and 2B). Malalignment of T11-T12 vertebral bodies with consequent subluxation and scoliosis was also noted.

Based on these imaging finding, a tentative diagnosis of hematogenous osteomyelitis was considered most likely. Less likely, differential diagnosis included round cell neoplasia, such as lymphoma, leukemia, multiple myeloma and histiocytic sarcoma. Post-contrast CT could have provided additional information regarding the possible site of infection or primary neoplastic lesion indicating the vertebral column changes as metastatic; unfortunately, establishing venous access was unsuccessful.

Due to the pathological fractures and grave neurological status, the patient was euthanized after CT examination and submitted for necropsy, further histopathology and microbiological culture testing.

A swab from the vertebral lesions was aseptically taken for aerobic, anaerobic and fungal culture. The swab was cultivated on Columbia agar (COL) with sheep blood (Thermofisher oxoid) and Columbia agar with sheep blood with added colistin and nalidixin acid (CNA) (Thermofisher oxoid) and incubated for 18 hours at 37°C with 5% CO_2. Another set of these plates was incubated for 18 hours at 37°C without O_2. The same swab was additionally cultivated on Mac Conkey agar (Thermofisher Oxoid) and incubated aerobically at 37°C for 18 hours and MALT and Sabouraud dextrose agar (Thermofisher oxoid) and incubated at 25°C. No bacterial or fungal growth was noted after 5 and 21 days, respectively.

Necropsy elucidated the extent of the pathological changes with the histopathology revealing a pyogranulomatous osteomyelitis. The affected vertebrae showed extensive osteonecrosis of the vertebral body

with loss of tissue, replacement with a variably dense organizing fibrovascular stroma and focal collapse and narrowing of the vertebral canal (Figure 3). The reactive stroma as well as the remaining marrow spaces were frequently infiltrated with degenerated neutrophils. Multifocally, there were nodular infiltrates of epithelioid macrophages surrounding neutrophils or small empty spaces. At the level of T5-T6, the spinal cord was severely compressed and diffusely necrotic with presence of hemorrhage (Figure 4). At the level of T11, there was frequent axonal degeneration and focal necrosis of the white matter. The adjacent skeletal muscle fibers were degenerated or atrophic, the interstitium expanded by fibrosis. Histochemical stains (PAS, Ziehl-Neelsen, Giemsa and Gram) showed no infectious agents. Based on the combination of the imaging findings, histopathology and absence of infectious agents, the diagnosis of CRMO was made.

DISCUSSION

The histomorphological features of the pathology in this prosimian are characteristic of chronic recurrent multifocal osteomyelitis described in human medicine. Although the name might suggest a chronic and recurrent course, the acronym itself is misleading, as this disorder does not necessarily present as chronic or recurrent and exhibits a wide spectrum of clinical presentations, including continuous type (Mallick, et al., 2016; Girschick et al., 2018). CRMO is an autoinflammatory disease described primarily in children and adolescent that is characterized by nonbacterial osteomyelitis (Jansson et al., 2007; Khanna, et al., 2009; Ferguson, 2016). The disease usually has a relapsing and remitting course with the etiology remaining elusive, although recent studies have suggested a genetic component (Cox and Ferguson, 2018). Possible immune mediated association secondary to previous or current infections elsewhere in the body has also been reported (Ferguson, 2016). Although CRMO is typically a disease with childhood onset, it can rarely also present in adults with several cases reported in the literature (Sato et al., 2017; Girschick et al., 2018; Mahady and Ladani, 2019).

In veterinary medicine, a case of multifocal pyogranulomatous osteomyelitis resembling CRMO in a lemur and involving the appendicular skeleton has been noted (Backues et al., 2001; Mcaloose and Stalis, 2011) but to the authors' knowledge, imaging features, including computer tomography features of histologically confirmed CRMO involving the vertebral column of a lemur have not been described yet.

CRMO is difficult to diagnose, primarily due to its variable presenting signs and broad differential diagnosis, including infection, primary benign or malignant osseous neoplasms and metastatic processes. In human medicine, in several case reports CRMO involving the vertebral column has been described (Martin et al., 1996; Baulot et al., 1998; Anderson et al., 2003; Gleeson et al., 2008), either as part of the multifocal disease or as a primary clinical complaint. A case of CRMO with subsequent spinal cord compression requiring anterior decompressive surgery and fusion with favorable outcome has been reported (Baulot et al., 1998). CRMO of the vertebral body is the most common site to be complicated by a pathological fracture in humans with radiographic findings including partial or complete loss in height of the vertebral body. None of the reported cases have shown extension of disease across the intervertebral disk space. Involvement of multiple noncontinuous vertebral bodies is common and can cause vertebra plana occurrence (advanced compression fracture) (Anderson et al., 2003; Khanna, et al., 2009). These described imaging features resemble the features of the patient of the present case with multifocal vertebral column involvement. In the present case, no additional lesions affecting the appendicular skeleton were noted; in particular no clavicular bone involvement, although the last mentioned location is often the primary site for CRMO in children.

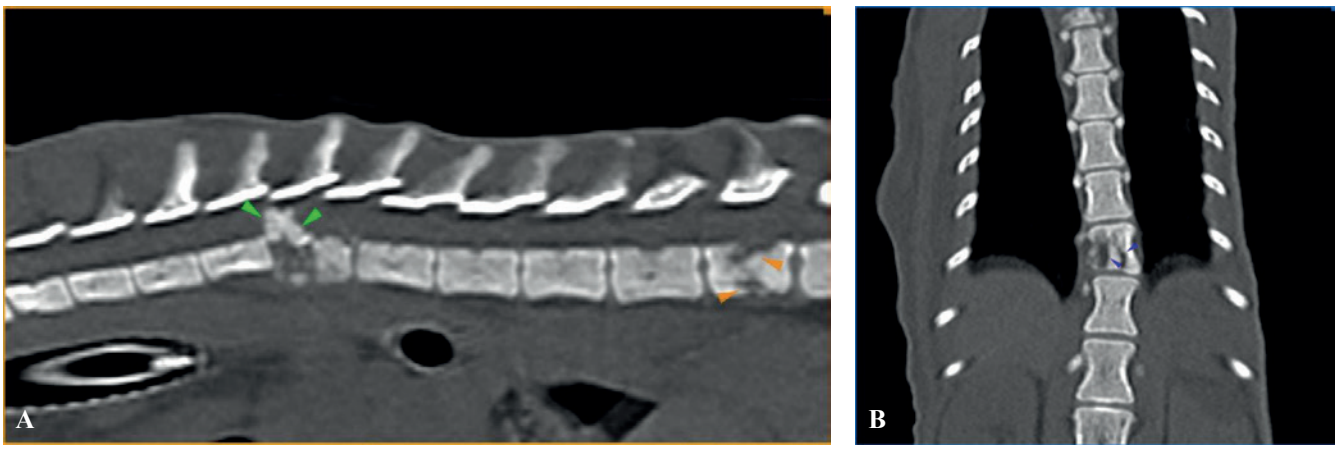

Figure 2. Sagittal and dorsal reconstructions showing A. Compression fracture of L5 and L6 with displaced fragments into the vertebral canal (green arrowheads) and fracture of the vertebral body of T11 (orange arrowheads) with subsequent scoliosis. B. Note the osteolytic lesions in T11 (blue arrowheads).

Similarly, the histology and histochemical stain results from this patient were consistent with sterile osteomyelitis. However, false-negative blood or biopsy cultures are common in patients in whom antibiotic therapy has been started (Braden et al., 1989; Braden, 1991; Tiemann et al., 2014; Gieling et al., 2019). The possibility that bacterial growth was inhibited by antibiotic therapy prior to biopsy and histopathology cannot be excluded, as the patient was treated with clindamycin (Griffiths and Bellenger, 1979). Additionally, previous investigations of sample techniques and specimen handling have revealed that suboptimal handling may be a reason for negative results as well (Rabillard et al., 2011). However, considering the fact that during the ongoing antibiotic treatment, worsening of the symptoms was seen, this was considered less likely.

Overall, prosimians are susceptible to a variety of bacterial infections but do not seem to have an increased susceptibility to any specific bacterial agent (Mcaloose and Stalis, 2011; Simmons and Gibson, 2012). Moreover, the clinical examination results of the lemur of the present case as well as the results of the bloodwork did not support the diagnosis of infectious disease process. However, in cases of chronic osteomyelitis, serum inflammatory markers may be normal (Lee et al., 2016), at least in human medicine. Additionally, in adults, hematogenous spread of infection is less common than in adolescents and children and is instead usually caused by continuous spread from soft tissue infections or direct inoculation. At the same time, when hematogenous spread does occur, it usually leads to vertebral osteomyelitis (Lee et al., 2016). Initial radiographs of the lemur did not show signs of osteolysis; however, bony lesions may not be evident radiographically in the initial stages of infection, as 50%-70% bone demineralization must occur before bone lysis can be observed on plain radiographs, which may take up to 21 days to be detected (Braden et al., 1989; Pineda, et al., 2009; Jaramillo, 2011).

Osteomyelitis in primates is most often caused by bacterial or fungal infections but appears to be an uncommon diagnosis with a prevalence of 0.8 % in free-ranging prosimians. The non-free-ranging environment does not seem to increase the risk of infectious osteomyelitis (Rothschild and Woods, 1992; Simmons and Gibson, 2012). A case of systemic *Yersinia pseudotuberculosis* as a cause of polyostotic osteomyelitis in a lemur has been described (Walker et al., 2018) with no overt evidence of underlying immunosuppression.

CONCLUSION

In conclusion, the authors believe that considering the CT characteristics of polyostotic vertebral body involvement, results of microbiological testing and histopathological results, the tentative post-mortem diagnosis of CRMO in the presented case is warranted.

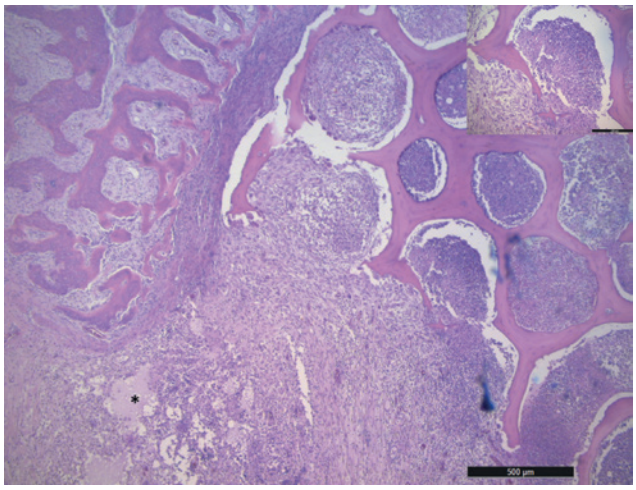

Figure 3. Histopathologic image showing a focus of severe inflammation (asterisk) destroying the vertebral bone with fibroplasia and reactive new bone formation (images upper left). Note retained marrow spaces filled with degenerated neutrophils (image upper right + inset).

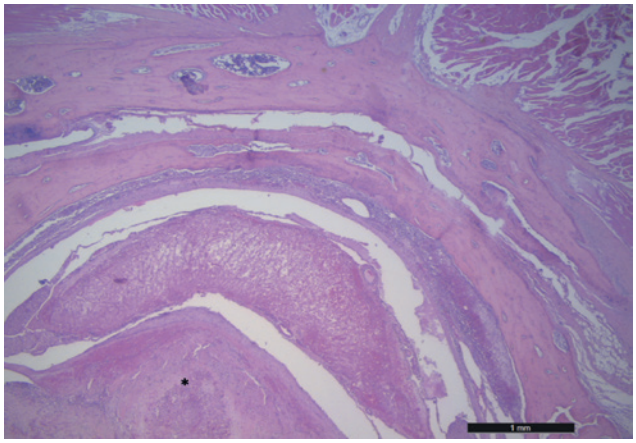

Figure 4. Histopathologic image showing collapse of the vertebral body and compression of the spinal cord at the level of T5-T6. The asterisk shows loss of bone from the vertebral body and replacement with a fibrovascular stroma. Note meningeal thickening due to inflammation and retained osseous structures of the vertebral arch and spinous process.

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