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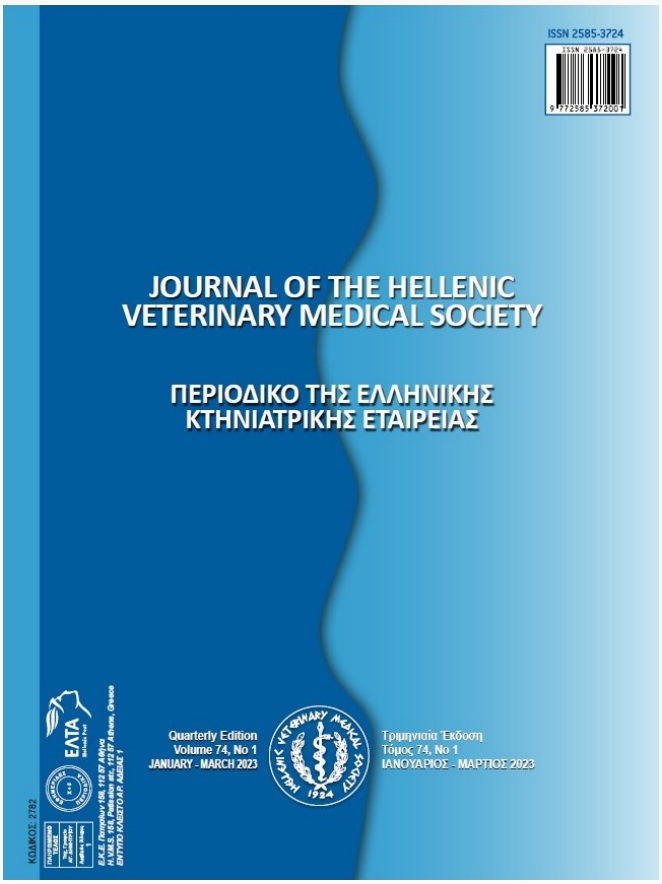

Mycobacterium genavense splenitis in a pet rabbit (Oryctolagus cuniculus) presented for fracture

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Case report
Κλινικό περιστατικό

Mycobacterium genavense splenitis in a pet rabbit (*Oryctolagus cuniculus*) presented for fracture

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ABSTRACT: Mycobacteriosis is an uncommon infection that has been sporadically described among wild, farmed and pet rabbits. To date, only one case of *Mycobacterium genavense* infection has been reported in a dwarf rabbit presenting with granulomatous pneumonia. This new case report describes granulomatous splenitis caused by *M. genavense* in a pet rabbit brought in for lameness caused by a femoral fracture. The initial blood test, X-ray, abdominal ultrasound, and bone marrow and spleen cytology results were consistent with a diagnosis of a metastatic giant-cell tumour.The rabbit underwent successful femoral osteosynthesis, and six months later, following the occurrence of a second spontaneous fracture and a worsening of overall health, the patient was euthanised. The *postmortem* histological examination showed severe granulomatous splenitis caused by acid-fast bacilli identified as *M. genavense* by real-time PCR analysis. The route of infection remains unknown, yet the lack of pulmonary involvement likely rules out airborne transmission. *M. genavense* infection, although rarely described in pet rabbits, appears to be an emerging pathogen and should be included among the differential diagnoses for pneumonia and splenomegaly.

Key words: rabbit; osteolysis; *Mycobacterium genavense;* multinucleated giant cells; case report

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Only one case of *Mycobacterium genavense* infection in a pet rabbit showing granulomatous pneumonia has been described thus far (Ludwig et al., 2009). We report a second case associated with granulomatous splenitis.

CASE HISTORY

A four-year-old intact lop doe presented with a one-week history of left hind limb non weight-bearing lameness. The rabbit lived indoors, and no history of trauma was reported. The appetite was conserved, yet the patient presented with a low body condition score, as well as mild left torticollis. According to the owner, the animal had been showing this abnormal head position for two years.

Hindlimb radiographs were taken, showing a simple closed oblique mid-diaphyseal left femoral displaced fracture. Multifocal polyostotic geographic lytic lesions affecting mostly the medulla of both hindlimbs and the pelvis associated with endosteal cortical lysis were also evident (Fig. 1). The polyostotic lytic lesions were considered consistent with neoplasia or systemic infectious processes. A full check-up including a biochemical analysis, complete blood count, complete radiographic study, and abdominal ultrasonography was thus performed. The complete blood count parameters were within the reference ranges. The biochemical analysis revealed hypoalbuminaemia (15 g/L, reference range 24-46 g/L (Washington & Van Hoosier, 2012)), hyperglobulinaemia (40 g/L, reference range 15-28 g/L (Washington & Van Hoosier, 2012)) and elevated alanine aminotransferase (ALT, 113 U/l, reference range 14-80 U/l ((Washington & Van Hoosier, 2012)).

Thoracic radiographs were performed to check for pulmonary metastases. Similar geographic osseous lytic lesions as described above were seen in both the right and left brachial/antebrachial bones (Fig. 2), in the ribs, in some dorsal spinous vertebral processes, in the neck of both scapulae, and in association with a mildly displaced costal fracture (Fig. 3). No pulmonary metastases were detected. Abdominal ultrasound

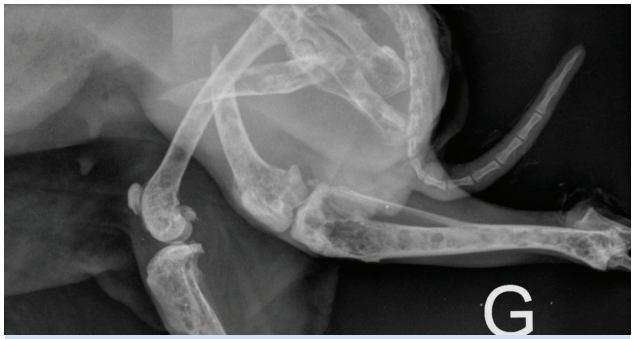

Figure 1: Lateral view of the pelvis and hindlimbs. Simple closed oblique mid-diaphyseal left femoral markedly displaced fracture. Multifocal polyostotic geographic lytic lesions affecting mostly the medulla of both hindlimbs and the pelvis are associated with endosteal cortical lysis.

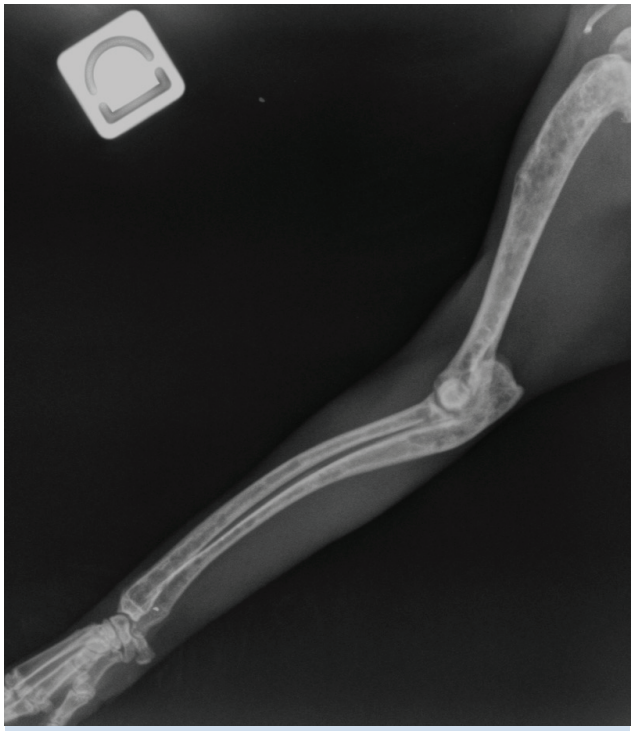

Figure 2: Mediolateral view of the right brachium and antebrachium (caudal part of humeral head is cut-off). Similar geographic osseous lytic lesions as described in the hindlimbs are observed in the humerus, radius and ulna.

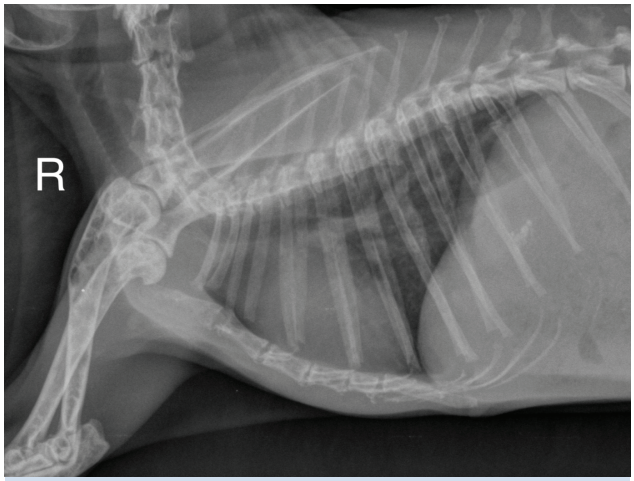

Figure 3: Right lateral view of the thorax. Similar geographic osseous lytic lesions as described in the hindlimbs are observed in both the right and left brachial/antebrachial bones, in the ribs, in several dorsal spinous vertebral processes, in the neck of both scapulae, and in association with a mildly displaced costal fracture. No pulmonary metastasis is detected.

examination revealed moderate splenomegaly. Under general anaesthesia, fine needle aspiration (FNA) was performed on the spleen and bone marrow of the right femur. The cytological exam showed severe splenic infiltration of a homogeneous population of multinucleated giant cells presenting heavily pigmented cytoplasm, consistent with haemosiderin. In the bone marrow, in addition to scattered myeloid tissue, a single multinucleated giant cell, similar to those found in the spleen, was observed. Cytological findings were considered consistent with a metastatic giant-cell tumour.

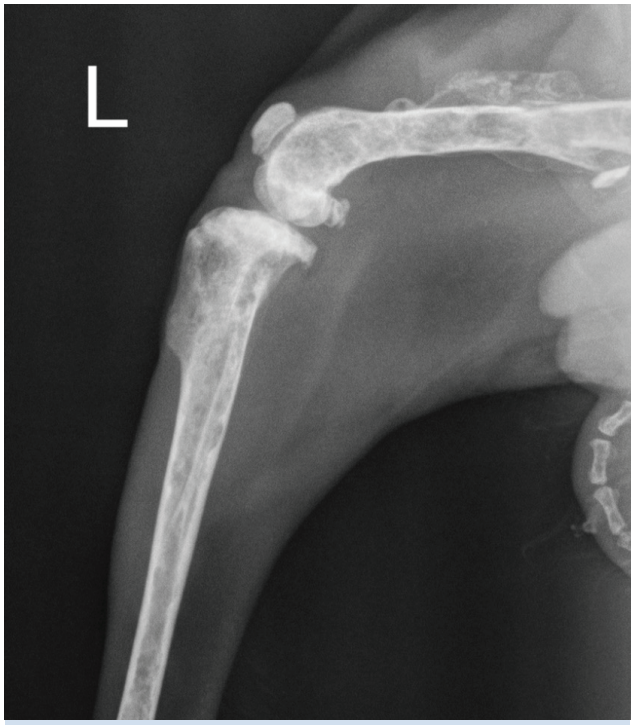

Figure 4: Mediolateral view of the left stifle including the femoral fracture site (control two months after surgery). Fairly good alignment of the femoral fragments with incomplete cortical bridging associated with heterogeneous smooth outlined periosteal proliferation (compatible with hypertrophic malunion). A small bone fragment is present at the proximal aspect of the fracture site (not seen in the first radiographs).

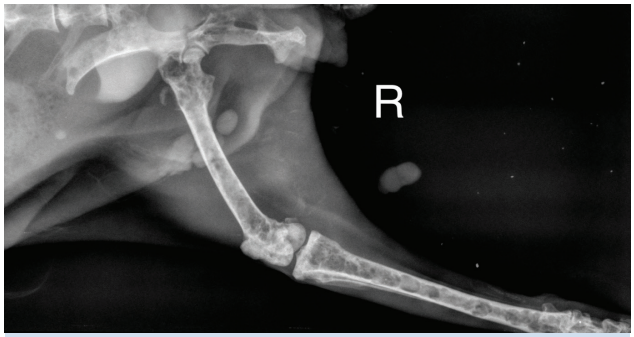

Figure 5: Oblique view of the right hindlimb, including the right half of the pelvis. A mildly displaced right acetabular fracture is observed. The polyostotic lytic lesions display no significant evolution. Moderate amounts of mineralized vesical sediments are also noted

At the owner's request, the patient underwent femoral osteosynthesis. A bone marrow core biopsy was proposed, but the owner declined the analysis. The patient was discharged with antibiotic (trimethoprim/sulfadiazine (Adjusol®) 30 mg/kg b.w., orally, BID) and anti-inflammatory (meloxicam (Metacam®) 1 mg/kg b.w., orally, SID) treatment for three weeks as well as prophylactic therapy for a presumptive *Encephalitozoon cuniculi* infection (fenbendazole (Panacur® 10%) 20 mg/kg b.w., orally, SID) for a full month.

Regular clinical examinations and blood tests were performed. One month later, the biochemical analysis showed a normalisation of the ALT and an increase in the albumin level (20 g/L, reference range 24-46 g/L (Washington & Van Hoosier, 2012)). The level of globulins remained elevated (41 g/L, reference range 15-28 g/L (Washington & Van Hoosier, 2012)). Serum protein electrophoresis was performed and showed a mild increase in γ-globulins (12.7%, reference range 8.6-9.6% (Melillo, 2013)).

Two months after surgery, the rabbit showed a normal gait, and the bone implants were removed. Control radiographs showed good alignment of the left femoral fragments with incomplete cortical bridging associated with peripheral heterogeneous smooth outlined periosteal proliferation (compatible with hypertrophic malunion) (Fig. 4). A previously undetected bone fragment was present at the proximal aspect of the fracture site. A mildly displaced right acetabular fracture was also noted (Fig. 5). The polyostotic lytic lesions displayed no significant evolution.

Six months after the first examination, the patient was euthanised following severe weight loss, a worsening of the polyostotic lytic lesions (increased in size and coalescent), and an incomplete pathological fracture of the right tibia (Fig. 6).

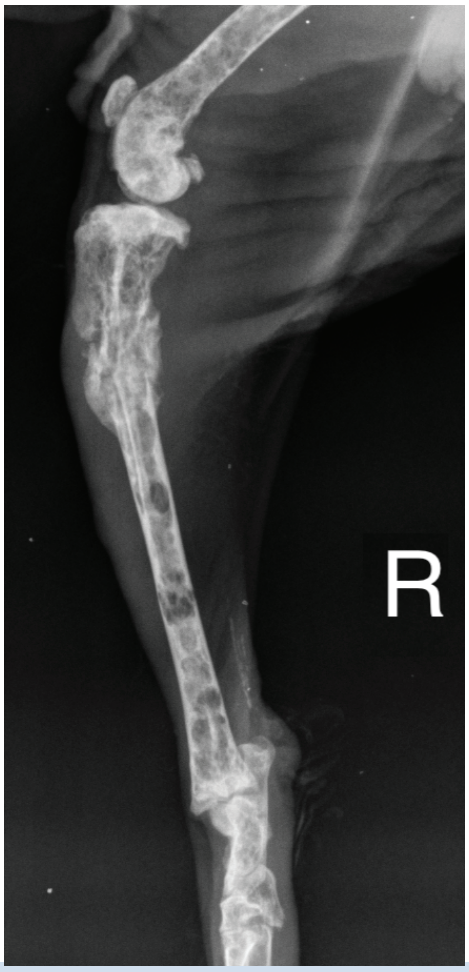

Figure 6: Mediolateral view of the right tibia, including the right stifle and tarsus, showing a worsening of the polyostotic lytic lesions (increased in size and coalescent) associated with an incomplete pathological fracture of the proximal tibial diaphysis with mild caudal angulation of the distal limb

At the necroscopic examination, splenomegaly was the only gross lesion observed. Samples from the spleen, liver, kidneys, uterus, and lungs, as well as fragments from the right tibia, were fixed in 10% neutral buffered formalin. Microscopic examination revealed marked extramedullary haematopoiesis characterised by a predominance of immature cells of the myeloid lineage in the spleen, liver, and kidneys. The bone marrow was hypercellular, and the granulocyte lineage was predominant, composed mainly of immature forms. The erythroid lineage was reduced, and few lymphocytes and plasma cells were identified. The parenchyma of the spleen was extensively obliterated by a severe accumulation of haemosiderin-laden macrophages and multinucleated giant cells (Fig. 7). On Ziehl-Neelsen staining, numerous acid-fast bacilli were identified in the cytoplasm of macrophages and multinucleated giant cells in the spleen (Fig. 8). Other tissues were histologically normal.

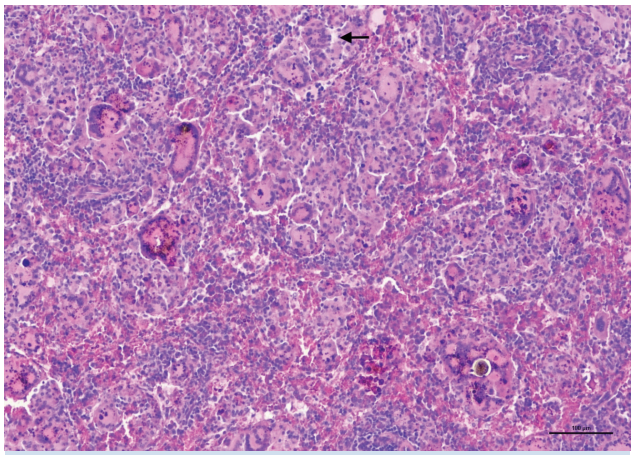

Figure 7: Photomicrograph of the spleen. The splenic parenchyma is diffusely and severely obliterated by macrophages and numerous multinucleated giant cells (arrow) containing a large amount of haemosiderin in their cytoplasm.
Haematoxylin-eosin staining (original magnification x10).
Courtesy of Dr A. Nicolier, Vetdiagnostic

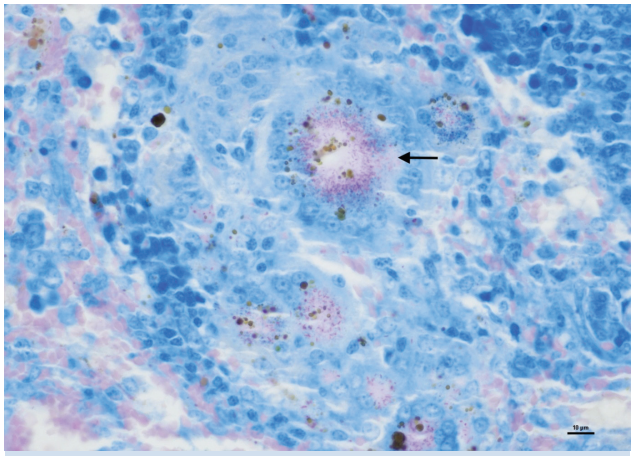

Figure 8: Photomicrograph of the spleen. Ziehl-Neelsen staining reveals numerous acid-fast bacilli in the cytoplasm of macrophages and giant cells (arrow).
Ziehl-Neelsen staining (original magnification x40).
Courtesy of Dr A. Nicolier, Vetdiagnostic

Real-time PCR (Real-time PCR *Mycobacteria* spp. Scanelis™) was performed on paraffin-wax-embedded samples from the spleen and tibial bone marrow and confirmed the presence of *M. genavense* in the former.

DISCUSSION

M.genavense, first isolated from HIV-infected patients in the early 1990s (Böttger, 1990), is a nontuberculous mycobacterium mainly found in zoological garden animals and pet birds, which are potential reservoirs (Böttger, 1990; Böttger et al., 1992; Böttger, 1994; Hoop et al., 1996; Tortoli et al., 1998; Tortoli, 2003; Manarolla et al., 2009; Gutierrez &Somoskovi,

2014; Haridy et al., 2014; Schmitz et al., 2018). Among domestic pet mammals, one case has been described in a dog (Kiehn et al., 1996) and another in a cat (Hughes et al., 1999). Among exotic mammals, *M. genavense* has been reported in ferrets (Dequéant et al., 2019; Lucas et al., 2000), in a giant grizzled squirrel (Theuß et al., 2010), in a chinchilla (Huynh et al., 2014) and in a domestic rabbit (Ludwig et al., 2009).

Spontaneous mycobacterial infections appear to be extremely rare in rabbits (Arrazuria et al., 2017; Gleeson &Petritz, 2020; Sevilla et al., 2020), although this species has been widely used as a research model for these pathogens (Arrazuria et al., 2017). Only four cases of mycobacterial infection in pet rabbits are currently reported in the literature (Ludwig et al., 2009; Klotz et al., 2018; Bertram et al., 2020), one of these being diagnosed among more than 2,013 retrospectively evaluated necropsies (Bertram et al., 2020).

The route of infection remains unclear, but research suggests water-borne and airborne transmission to be likely (Portaels et al., 1996; Hillebrand-Haverkort, 1999; Ludwig et al., 2009; Schrenzel, 2012). Furthermore, over the years, mycobacteriosis has been described in immunocompromised humans and cats, suggesting the influence of immune status on mycobacterial infection susceptibility (Böttger, 1990; Hughes et al., 1999; Krebs et al., 2000; Hoefsloot et al., 2013; Henkle& Winthrop, 2015; Wu & Holland, 2015; Bourlon et al., 2017). In our patient, the presumed encephalitozoonosis could have been a potential cause of immunosuppression (Ludwig et al., 2009).

The disease seems to follow a course of several months (Klotz et al., 2018; Bertram et al., 2020), and the clinical signs described in pet rabbits are poor nutritional status associated with intermittent diarrhoea and pneumonia (Ludwig et al., 2009; Klotz et al., 2018; Bertram et al., 2020). Mycobacteriosis generally evolves as a disseminated infection, and the affected organs are usually the spleen, liver, lungs, lymph nodes, skin, and conjunctiva (Kiehn et al., 1996; Hughes et al., 1999; Lucas et al., 2000; Moreno et al., 2007; Ludwig et al., 2009; Huynh et al., 2014; Klotz et al., 2018; Dequéant et al., 2019; Bertram et al., 2020). In domestic rabbits, however, *M.genavense* has currently been isolated only in the lungs (Ludwig et al., 2009). In our patient, the rabbit initially presented with lameness caused by a presumed spontaneous femoral fracture, and over the course of the disease, other symptoms were nonspecific and mainly involved intermittent diarrhoea and weight loss.

The biochemical abnormalities detected through bloodwork were considered secondary to either the bone lesions or malignancy-related inflammation. Indeed, increased ALT is mainly seen with tissue damage rather than with liver disorders in rabbits (Melillo, 2007), making the multiple bone lesions detected radiographically the most likely cause of parameter elevation in our patient. Second, differential diagnoses for hypoalbuminaemia in rabbits include chronic inflammation, chronic malnutrition due to either poor diet or advanced dental disease, liver disease, protein-losing nephropathy such as glomerulonephropathy, and protein-losing enteropathy (Melillo, 2007). In our patient, no renal, hepatic, or gastrointestinal abnormalities were detected in either the general examination or the abdominal ultrasound, making organ-failure-related hypoalbuminaemia unlikely. Therefore, the hypoalbuminaemia was attributed to the chronic inflammation associated with either the bone lesions or a malignant process. However, it should be noted that no urinalysis was performed; consequently, glomerulonephropathy could not be entirely excluded. Finally, hyperglobulinaemia and hypergammaglobulinaemia are found in inflammatory conditions (Melillo, 2007, 2013) and, in our patient, would be compatible with the aforementioned chronic inflammation.

Granulomas containing acid-fast microorganisms are the hallmark of mycobacterial infections and are generally found within the affected organs (Sakamoto, 2012; Shah et al., 2017; Klotz et al., 2018; Bertram et al., 2020; Pennington et al., 2021). In our patient, the initial cytological analysis of the spleen showed a homogeneous population of multinucleated giant cells with no detected aetiological agent, making the diagnosis of an atypical giant-cell granuloma unlikely. These features associated with clinical presentation, medical imaging, and the detection of multinucleated giant cells in bone marrow were instead considered consistent with a presumptive metastatic giant cell tumour.

However, a definitive diagnosis of mycobacteriosis was eventually reached upon *postmortem* histological examination of the spleen. The initial failure to identify the pathogen through FNA could be due to a low number of microorganisms within the sample or to the lower sensitivity of cytology than of histology for mycobacterial detection (Suri et al., 1998; Wangai et al., 2017). Furthermore, neither *antemortem* cytology nor *postmortem* histology revealed the presence of microorganisms in bone marrow samples. This could indicate an actual lack of mycobacteria within the

samples, or it could be spurious due to the technical difficulty of detecting mycobacteria. In fact, research shows that mycobacteria are detected in less than 50% of bone marrow histological examinations (Marques et al., 2000). Finally, sample mishandling should also be considered, as no signs of osteomyelitis were identified in the microscopic analyses, despite the presence of multiple osteolytic lesions in the radiographs.

Given the final diagnosis, the presence of multinucleated giant cells within the bone marrow may suggest that the bone was infiltrated by the same granulomatous process affecting the spleen. Osteomyelitis and bone lesions have been reported in mycobacteria-infected pygmy rabbits (*Brachylagus idahoensis*) (Harrenstien et al., 2006) and in a rabbit with intestinal mycobacteriosis presenting with multiple pelvic bone fractures and weight loss (Bertram et al., 2020). Moreover, mycobacterial osteomyelitis has been described in humans (Wu & Holland, 2015; Bourlon et al., 2017) and in several families of birds and mammals (Portaels et al., 1996; Thorel et al., 1997). A retrospective radiographic study showed that cats with confirmed mycobacteriosis had osteolytic lesions in 73% of cases (Bennett et al., 2011). Nevertheless, the radiographic appearance of these lesions is not specific and may be confused with neoplastic processes (Bennett et al., 2011; Langley-Hobbs & Harcourt-Brown, 2013; Selçuk et al., 2014).

The diagnosis of mycobacterial infection is challenging, and clinical examination, blood testing or medical imaging alone are usually insufficient. A combination of the previously cited means along with microscopic demonstration of bacilli is often required for a definitive diagnosis. However, although the gold-standard tests for this disease are either bacterial culture or molecular testing (Kobayashi, 2014), mycobacteria show fastidious growth requirements, and in a previous study, successful isolation and culture of *M.genavense* occurred in only 50% of cases (Böttger, 1994). In our patient, as mycobacteriosis was not initially suspected, no culture was performed. Nevertheless, the pathogen was isolated *postmortem*, using real-time PCR, in spleen samples but not in bone marrow samples. As discussed earlier, this could indicate either the absence of mycobacteria in the bone sample or a false-negative error caused by technical limitations. Real-time PCR is considered highly specific but shows only approximately 60% sensitivity under optimal conditions (Al-Zamel, 2009), and the formalin sample fixation method we used has been shown to further decrease sensitivity (Rish et al., 1996; Krebs et al., 2000; Bourlon et al., 2017; Vitošević et al., 2018; Elghoul et al., 2020).

In contrast to the previous case report on *M.genavense* infection described in a rabbit (Ludwig et al., 2009), pulmonary lesions were absent in our patient, and the spleen was the only organ among the analysed samples in which the infectious agent was isolated. Therefore, the lack of pulmonary involvement does not support airborne transmission in this report. However, although no intestinal abnormality was detected with ultrasound or visualised macroscopically during necropsy, oral transmission cannot be excluded, as the intestines were not examined histologically.

Splenomegaly is not a common finding in rabbits, and differential diagnoses include tumours (Ishimori et al., 2017; Bertram et al., 2021), infections with viruses such as rabbit haemorrhagic disease virus (Abrantes et al., 2012; Harcourt-Brown et al., 2020) and infections with bacteria such as *Francisella tularensis* (Reed et al., 2011) or *Yersinia pseudotuberculosis* (Chassang et al., 2019). *Mycobacterium avium* has also been identified as the causative agent of granulomatous splenitis together with caecal, lymph node, hepatic, and pulmonary lesions in dwarf rabbits (Bertram et al., 2020). According to our findings and those described in a previous case report (Ludwig et al., 2009), *M.genavense* infection, although rare, should be included among the differential diagnoses for pneumonia and splenomegaly in pet rabbits.

Humans are susceptible to *M.genavense* infection, and close contact with pets showing nonspecific signs as well as the chronic course of this disease could represent a potential zoonotic threat (Bertram et al., 2020; Klotz et al., 2018). Because of this risk, the treatment of mycobacterial infection, while shown to be successful in two ferrets (Lucas et al., 2000), may not be appropriate, and euthanasia should be considered instead. For this patient, the owners declined undergoing medical examination despite being warned of the potential zoonotic threat.

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CONFLICT OF INTEREST

None declared by the authors.

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