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Mycobacteriosis in small animals

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Submitted by

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Declaration of Authenticity

I hereby declare that I have written this thesis independently and that I have not used any other sources and aids other than those listed. All text passages taken from other sources have been cited.

I have carried out the decisive work myself and have listed all contributors with their contributions to the work.

This thesis has not been submitted or published elsewhere.

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Sarah Pross

Abstract

To date, mycobacteriosis in small animals has only been sporadically documented, primarily in the context of case reports or case series. Therefore, practitioners often do not include mycobacteriosis in their list of differential diagnoses. Medical records of small animals from the Pathology of the University of Veterinary Medicine Vienna, the Pathology Service of the Schwarzman Animal Medical Center in New York, and the Institute of Animal Pathology of the Freie Universität Berlin were searched retrospectively for cases of proven or suspected mycobacteriosis. Twenty-two cases, in which histopathological findings including Ziehl-Neelsen staining of biopsy or necropsy samples suggested mycobacteriosis, were included in the retrospective study. Data on medical history, clinical signs, further diagnostics, PCR, and sequence analysis, histopathology, treatment, and outcome were analyzed if available. PCRs and sequence analysis were successfully performed in 21 cases. One case was confirmed by culture only. Among the 22 cases, 14 were cats, four rabbits, three ferrets, with one case each involving a dog and a chinchilla. All detected mycobacteria belonged to the non-tuberculous mycobacteria (NTM), with M. avium (n = 14) being the most frequently detected. Most common signs observed during the clinical examination were gastrointestinal disorders (n = 12), abdominal masses (n = 5), peripheral lymphadomegaly (n = 4), respiratory signs (n = 4) and dehydration (n = 4). Several animals showed unspecific signs. Only one cat was treated with specific antimycobacterial therapy (triple antibiosis), but therapy was not successful because of the advanced stage of the disease. Only one patient gained remission, the others were either euthanized, deceased, or data was not available. The conclusion of this report is to highlight, that although it is a rare disease, mycobacteriosis should be considered as differential diagnosis not only in animals with cutaneous signs but also with gastrointestinal signs, respiratory signs or lymphadenomegaly and abdominal masses particularly when cytology or histopathology reveals a (pyo-)granulomatous inflammation. In suspicious cases, Ziehl-Neelsen staining to detect acid-fast bacteria should be initiated. If positive, confirmation of mycobacteria should be performed by PCR or culture. The results indicate that the prognosis for a mycobacterial infection should be considered guarded.

Zusammenfassung

Mykobakteriose bei Kleintieren wurde bisher nur selten in Fallberichten oder Fallserien dokumentiert und wird daher in der Praxis oft nicht als Differentialdiagnose berücksichtigt. Die Krankenakten von Kleintieren der Pathologie der Veterinärmedizinischen Universität Wien, des Pathologischen Dienstes des Schwarzman Animal Medical Center in New York und des Instituts für Tierpathologie der Freien Universität Berlin wurden retrospektiv nach Fällen von nachgewiesener oder vermuteter Mykobakteriose durchsucht. In diese retrospektive Studie wurden 22 Fälle aufgenommen, bei denen eine pathohistologische Untersuchung von Biopsien oder Autopsien vorlag und die Ziehl-Neelsen-Färbung einen positiven Nachweis von säurefesten Stäbchen ergab. Sofern verfügbar, wurden Daten zur Anamnese, zu klinischen Symptomen, zur weiteren Diagnostik, zur PCR- und Sequenzanalyse, zur Histopathologie, zur Behandlung und zum Outcome analysiert. Vierzehn Katzen, vier Kaninchen, drei Frettchen, ein Hund und ein Chinchilla waren betroffen. PCRs und Sequenzanalysen wurden in 21 Fällen erfolgreich durchgeführt- ein Fall wurde nur mittels Kultur bestätigt. Alle nachgewiesenen Mykobakterien gehörten zu den nicht-tuberkulösen Mykobakterien (NTM), mit *M. avium* (n = 14) als häufigstem Erreger. Die häufigsten Anzeichen bei der klinischen Untersuchung waren gastrointestinale Symptome (n = 12), abdominale Massen (n = 5), periphere Lymphadenomegalie (n = 4), respiratorische Symptome (n = 4) und Dehydratation (n = 4). Mehrere Tiere zeigten unspezifische Anzeichen. Nur eine Katze erhielt eine spezifische antimykobakterielle Therapie (Dreifachantibiose), die jedoch erfolglos blieb. Die meisten Tiere wurden euthanasiert, verstarben oder es lagen keine Daten zum weiteren klinischen Verlauf vor. Nur bei einem Patienten kam es zu einer Remission. Diese Studie zeigt, dass Mykobakteriose als Differentialdiagnose nicht nur bei Tieren mit kutanen Symptomen, sondern auch bei gastrointestinalen oder respiratorischen Symptomen sowie Lymphadenomegalie und abdominalen Massen in Betracht gezogen werden sollte, vor allem wenn in der Zytologie oder Histopathologie eine (pyo)-granulomatöse Entzündung nachgewiesen wird. Bei Verdacht sollte eine Ziehl-Neelsen-Färbung zum Nachweis säurefester Bakterien durchgeführt werden und wenn diese positiv ist, anschließend eine PCR oder Kultur. Die Ergebnisse zeigen, dass die Prognose einer Mykobakteriose als

vorsichtig einzustufen ist.

List of abbreviations

NTM	Non-tuberculous mycobacteria
MBT	Mycobacterium tuberculosis complex
MAC	Mycobacterium avium complex
FNA	Fine needle aspiration
GI	Gastrointestinal
Lap	Lymphadenopathy
Resp	Respiratory
Orth	Orthopedic
S	Symptomatic therapy
AB	Antibiotics
GC	Glucocorticoids
ESH	European Shorthair cat
Fs	Female spayed
Mn	Male neutered
F	Female
M	Male
Deh	Dehydration

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1 Introduction

Mycobacteriosis is a chronic infection caused by bacteria that belong to the order of Actinomycetales, family Mycobacteriaceae. The genus Mycobacteria include aerobic, non-spore forming, nonmotile, intracellular, acid-fast, pleomorphic bacterial rods with differences between the species regarding pathogenic potential and host affinity (1).

Mycobacteria are categorized into two main groups: the tuberculous mycobacteria (MBTC), which are obligatory pathogenic bacteria and the non-tuberculous mycobacteria (NTM) (1).

1.1 Tuberculous mycobacteria (MBTC)

In 2022, 7.5 million new cases of tuberculosis (TB) have been diagnosed in humans worldwide. Currently, the total amount of tuberculosis in humans has been estimated to be 10.6 million, the highest number since tuberculosis figures have been monitored in 1995. The disease has been associated with 1.3 million deaths in 2022. TB remained the world's second leading cause of death from a single infectious agent. Approximately 5-10 % of individuals infected will exhibit clinical signs (2). The treatment for tuberculosis in humans is very extensive including four to five medications and should be continued over a long period (3). 1.4 % of the cases were estimated to have zoonotic origin (4).

The MBTC consists of ten species. For small animals relevant species include *M. bovis*, *M. microti* and *M. tuberculosis* (1). Cats show a natural resistance against *M. tuberculosis* (5).

1.2 Non-tuberculous mycobacteria (NTM)

The NTM group consists of slow growing (growth in culture takes from seven days to three months), fast-growing (growth in culture takes less than seven days), and fastidious mycobacteria. Fastidious mycobacteria cannot be cultured by routine culture methods due to special requirements for bacterial growth (1). In contrast to the obligate pathogenic tuberculosis pathogens, NTM live saprophytically and are found in the environment including soil, dust, water sources such as drinking water, natural bodies of water, showers, pools, whirlpools, sanitary facilities and water distribution systems (7). It is possible to become infected by cutaneous inoculation through traumatic or surgery wounds, by inhaling aerosols from NTM-contaminated water or soil dust, or orally. NTM can survive in drinking water for a long time as they are oligotrophic, survive in biofilms, are highly resistant to disinfectants, grow at low oxygen levels and can parasitize intracellularly in protozoa (8, 9) .

Humans infected with NTM are often immunosuppressed (e.g. AIDS patients) and develop a disseminated disease (10). However, the number of patients with NTM associated lung diseases is increasing in the non-AIDS population (11). MAC infections in animals are also often correlated with immunosuppression (12, 13).

NTM infections in cats and dogs usually lead to skin disease, mostly in form of localized skin nodules, with the exception of Mycobacterium avium complex (MAC), which is often associated with systemic disease (14, 12, 15–17, 4). Slow-growing NTM cause pyogranulomatous cutaneous or disseminated disease in dogs and cats (18–20). Rapidly-growing NTM usually cause pyogranulomatous panniculitis, but pneumonia or disseminated infections in dogs and cats have also been described in case reports (21–24). Cats infected with *M. microti*, NTM and mycobacteria that cause feline leprosy show skin lesions like non-painful skin nodules, non- healing wounds, draining tracts and ulceration on head, limbs, trunks and enlargement of regional lymph nodes (25–27). But unlike other NTM, *M. avium* infections often lead to systemic disease. Manifestation of systemic MAC infection in cats is typically characterized by gastrointestinal and respiratory signs as well as lymphadenopathy (16, 28). Other signs which occur sporadically in NTM include ocular disorders, mostly uveitis and blindness, but also fever, spleno- and hepatomegaly, bone lesions and neurological disease (29, 30). Pathogens that cause feline leprosy are fastidious mycobacteria that are not necessarily phylogenetically related and form a heterogeneous group. Mycobacteria that cause feline leprosy include *M. lepraemurium, Candidatus M. lepraefelis and Candidatus M. tarwinense, M. visible* (6).

In dogs infected with NTM cutaneous lesions are common (31–33). MAC infections in dogs are commonly systemic, most dogs show non-specific systemic signs such as lethargy, weight loss and fever, and others chronic gastrointestinal signs (34–36). Abdominal ultrasonography often reveal generalized lymphadenopathy, hepatopathy and/or splenomegaly, other possible signs are osteomyelitis, polyarthritis or cutaneous disease (37–39, 36).

Rabbits with NTM infection can show respiratory and gastrointestinal signs, abdominal masses, orthopedic signs and lymphadenopathy (40–43).

Ferrets infected with nontuberculous mycobacteria show ocular- , respiratory-, gastrointestinal signs, and lymphadenopathy (44, 45) .

There are only four case reports of chinchillas with confirmed or suspected mycobacterial infection. One showed emaciation (46). Another one had prolonged vaginal discharge. Histopathology showed pyogranulomatous metritis and granulomatous inflammation in various organs (47). Another chinchilla that had given birth three weeks before, presented with anorexia and lethargy. Granulomatous lesions were found in multiple organs at post mortem examination (48). In a case report of a group of five chinchillas from Japan, three showed respiratory signs. Mycobacteriosis was suspected due to necropsy results that revealed caseous nodules. Pathohistology showed granulomatous inflammation and acid- fast rods were detected by special staining. However, no mycobacteria could be detected by PCR and culture (49).

2 Material und methods

2.1 Case selection

Only small animal cases (dogs, cats, small mammals hold as companion animals) in which histopathologic examination of biopsies or necropsies was available and Ziehl-Neelsen staining revealed acid-fast rods were included in the retrospective study. A total of 22 cases fulfilled these criteria including nine from the Pathology of the University of Veterinary Medicine Vienna, seven from the Institute of Animal Pathology of the Freie Universität Berlin and six from the Pathology Service of the Schwarzman Animal Medical Center in New York. The medical histories of two rabbits from Berlin, one cat from New York and one cat from Vienna have already been published in case reports (Nos. 4, 5,12,19). (41, 14, 23) One case report of a cat from Vienna was submitted for publication at the time of finishing the diploma thesis (No. 20). Medical history, clinical signs, further diagnostics (imaging, hematology, biochemistry, cytology and parasitological examinations), PCR, treatment and outcome were included if available.

2.2 Treatment

Treatment was classified into surgical, antibiotic, glucocorticoid, and non-specific therapy. The different therapeutical approaches are listed in table 1. Surgery was carried out in cases of localized skin or subcutaneous lesions or masses, either to completely excise them or to obtain a diagnostic sample. Antibiotic treatment of suspected mycobacterial infections included appropriate antimicrobials that were administered individually or in combination. Nonetheless, the treatment, including antibiotics, was usually non-specific and targeted specifically against mycobacteria in only one case (No. 4). Glucocorticoid therapy comprised prednisolone and dexamethasone. However, no uniform dosage regimen was used due to the respective nature of the study. Non-specific therapy predominantly included analgesics, antiemetics, gastric protectants, infusions, and feed supplements.

2.3 Histopathology

In total, histopathology was performed in 22 animals. A dissection of the entire animal body was performed in 14 animals [Nos. 2, 9, 10, 11, 15 and 19 (cats), Nos. 8 and 17 (ferrets), Nos. 5, 6, 12 and 13 (rabbits), No. 14 (dog), No. 22 (chinchilla)]. Biopsies were available in eight cases: three skin biopsies of different animals were examined (cat No. 21 and No. 18, ferret

No. 7), two lymph node biopsies (cat No. 4 and No. 20), and three other biopsies were available. These biopsies included a biopsy of a circumferential proliferation of the right caudal complex of the mammary gland (cat No. 1), a biopsy of soft tissue and bone of the oral cavity (cat No. 3) and a biopsy of an intraluminal tracheal circumferential proliferation (cat No. 16). In addition, a cytology following FNA of lymph nodes was performed in five animals [No. 4, No. 20, No. 21 (cats); No. 14 (dog); No. 17 (ferret)], a cytological examination of a skin probe in one cat (No. 18) a cytology of a jejunal mass in one case (cat No. 2), and a cytological examination following liver puncture in one dog (No. 14). Ziehl-Neelsen staining was positive for all 22 histopathological samples.

2.4 Molecular detection and Ziehl- Neelsen staining

PCR was performed in a total 21 cases, 17 of them retrospectively in Vienna. In case No. 19 mycobacteriosis was confirmed by culture only. 17 PCRs were positive immediately, four others (Nos. 1, one of two samples of 3, 7 and 20) were positive after repeated PCR was performed with an increased number of cycles. After three PCRs, which were initially negative for mycobacteria, turned positive when performed with an increased number of cycles, it may be advisable to conduct PCR with an increased number of cycles again in doubtful cases. In case No. 20, the bacterial load was too low. Therefore, the Ziehl-Neelsen staining that was carried out first, was negative. Another Ziehl-Neelsen staining performed in deeper sectional layers revealed few macrophages with positively stained intracytoplasmic rods. Culture was performed four times, three times in addition to the PCR Results (Nos. 4, 9, 12).

3 Results

3.1 Signalement

With 13 patients, the species cat was most frequently represented, followed by four rabbits and three ferrets and one dog and chinchilla each. Complete medical histories were available in 19 cases, clinical examinations were documented in 14 cases.

Six of 13 cats were European Shorthair, followed by three British Shorthair, one European Longhair, one Abyssinian cat, one Siamese-mix and one unknown breed. Two of the four rabbits were dwarf rabbits, one was an angora rabbit and one a tan-rabbit. The dog was a dachshound-mix (Table 1).

Five cats were male castrated, and five females spayed. One was male and the gender of two cats were unknown. Two rabbits were female spayed, one male castrated and one female. One ferret was female, one male and the third male castrated. The dog and the chinchilla were both male (Table 1).

The age of the cats of the present study ranged from nine months to 18 years, with an average age of 5.6 years and a median age of four years. Among the rabbits, age ranged from two to five years, with an average age of 3.3 years and a median age of three years. The ferrets were between four and seven years old, with an average age of five years and a median age of four years. The dog was 13 months old, while the chinchilla was five years old (table 1).

Six cats lived exclusively indoors, two had outdoor access, and one had outdoor access while on a leash. In four cats it was unknown whether the animals had outdoor access. Two rabbits had outdoor access, while housing conditions were unknown in the other two rabbits.

3.2 Clinical examination

The most common reason for presentation were gastrointestinal signs (n = 8), followed by neurological signs (n = 4) and lethargy (n = 4), respiratory disorders (n = 3), orthopedic signs (n = 2) and others (ocular, chronic tooth fracture, shock, reduced water intake) (table 1).

Most common signs noted through clinical examinations were gastrointestinal signs (n = 12), abdominal masses (n = 5), peripheral lymphadomegaly (n = 4), respiratory disorders (n = 4), dehydration (n = 4). Animals with gastrointestinal signs included six cats, three rabbits, two ferrets and one dog. Enlargement of palpable lymph nodes and respiratory disorders were observed in three cats and one ferret. Most patients showed a combination of several different clinical signs (table 1).

Other clinical signs that were noted included cutaneous lesions (n = 3), neurological disorders (n = 3), orthopedic problems (n = 2), icteric mucous membranes (n = 2), subcutaneous masses (n = 2) and reduced general behaviour (n = 2). In addition, ocular signs were also observed in one cat (No. 10) (table 1).

Table 1

Overview of the species, sex, age, physical complaint, therapy and the outcome of mycobateriosis.

No.	**Pathology**	**Species**	**Sex**	**Age In years**	**Physical complaint**	**Therapy**	**Outcome**
1	Berlin	cat	-	-	Mammary gland mass	surgery	-
2	New York	cat	fs	14	Lethargy, GI-signs	GC, Cytostatic drug (lymphoma)	Euthanasia
3	New York	cat	mn	18	Chronic tooth fracture with pulp involvement	-	-

4	Vienna	cat	mn	2	fever, GI- signs, abd. mass, lap, apathy, deh	Triple AB, S	Euthanasia
5	Berlin	rabbit	f	2	GI- and orth signs	-	Euthanasia
6	Vienna	rabbit	mn	3	Neurological signs, abd. mass	S	Deceased
7	Vienna	ferret	m	4	Repeatedly bleeding cutaneous mass; 2 ½ years later abdominal mass (no further diagnostics)	S	Euthanasia
8	Vienna	ferret	f	7	anemia, abd. mass, GI- and neurological signs, apathy	S	Euthanasia
9	Berlin	cat	fs	3	lap, abd. mass, jaundice, neurological signs	AB, GC, S,	Euthanasia
10	New York	cat	m	0,75	Fever, GI-, ocular and resp signs, abd. mass, lap, deh	S	Euthanasia

11	New York	cat	mn	8	GI- and neurological signs	-	Euthanasia
12	Berlin	rabbit	fs	5	Shock, abd. mass, emaciation, lap	-	Euthanasia
13	Berlin	rabbit	fs	3	Emaciation, GI-signs	AB	Euthanasia
14	Vienna	dog	m	1	GI- and resp signs, lap, emaciation, apathy, anemia, jaundice, deh	S, AB	Euthanasia
15	Vienna	cat	fs	6	GI- signs, lap, jaundice, deh, abd. mass, emaciation	No therapy	Euthanasia
16	New York	cat	mn	4	Resp signs	S, GC, AB	-
17	Vienna	ferret	mn	4	Apathy, GI-, orth, and resp signs, lap	S, GC	Euthanasia
18	Berlin	cat	fs	4	Cutaneous signs	Surgery, AB	-
19	New York	cat	mn	4	Resp signs, emaciation	AB (double than single)	Deceased
20	Vienna	cat	mn	1	Lethargy, lap, GI-signs	S, AB	Remission

21	Berlin	cat	-	-	Lap, cutaneous lesions	S	-
22	Vienna	chinchilla	m	5	emaciation, anemia, GI- signs, lap	-	Euthanasia or Deceased

Abbreviations

N	Assignment number of the animal
GI	Gastrointestinal
Lap	Lymphadenopathy
Resp	Respiratory
Orth	Orthopedic
S	Symptomatic therapy
AB	Antibiotics
GC	Glucocorticoids
ESH	European Shorthair cat
Fs	Female spayed
Mn	Male neutered
F	Female
M	Male
Deh	Dehydration

3.3 Signalement and predisposing factors

One cat was assumed to be immunosuppressed because of cytostatic therapy against lymphoma (No. 2). The cat received asparaginase once as well as chlorambucil and prednisolone for a long time. One ferret was also under potential immunosuppressive treatment (No. 17). It received prednisolone (1 mg/kg p.o. twice daily, Prednicortone® Dechra, Northwich, United Kingdom) for eleven days until it was euthanized due to its deteriorating clinical condition. Comorbidities were observed in one cat with chronic kidney disease and in a cat with lymphoma (Nos. 2, 11).

3.4 Further examination

3.4.1 Hematology

Hematology was available in eight animals. The patients included five cats, two ferrets and one dog. One cat (No. 4) showed mild anemia with a hematocrit of 26.8 % (reference interval 27.0 % to 47.0 %) and another cat (No. 2) a more distinct anemia with a hematocrit of 24.5 % which worsened to a hematocrit of 12.4 % (reference interval: 30.3 % to 52.3 %). Cat No. 2 had a leucocytosis of 24.54 K/µL (2.87 - 17.02 K/µL), a neutrophilia with 20.57 K/µL (reference interval 2.30 - 10.29 K/µL), a monocytosis 2.21 K/µL (reference interval 0.05 - 0.67 K/µL) and thrombocytosis of 741 K/µL (151 - 600 K/µL). Cat No. 19, showed a leukocytosis (18.300 cells/ml) with neutrophilia (14.091 cells/ml) and monocytosis (2.196 cells/ml) (23). Serum amyloid A (SAA) was monitored in one cat (No. 20), it decreased as clinical signs improved and abdominal lymph node enlargement was not detectable by ultrasound examination anymore. Additionally, it showed leucocytosis 22.88 K/µL (reference interval 2.87 - 17.02), neutrophilia 16.72 K/µL (reference interval 2.30 - 10.29 K/µL), 0.97 K/µL (reference interval 0.05 - 0.67 K/µL) and basophilia 0.42 K/µL (reference interval 0.01 - 0.26 K/µL). The dog (No. 14) had nonregenerative anemia and hematocrit declined from 24.0 % to 22.3 % within two days (reference interval 37.3 % to 61.7%). The dog also had a leukocytosis of 28.06 K/µL which increased to 32.59 K/µL (reference interval from 5.05 to 16.76 K/µL), more specifically it showed a neutrophilia with 22.93 K/µL (reference interval 2.95-11.64) and a monocytosis 2.88 K/µL (reference interval 0.16-1.12 K/µL, and it was thrombocytopenic with 130 K/µL platelets (reference interval 148-484 platelets). The blood count of one ferret (No. 8) revealed mild anemia (Hematocrit 31%), while no changes were observed in another ferret (No. 17). Out of five cats that were tested for FIV and FeLV infection, all were negative.

3.4.2 Abdominal ultrasonography

Six animals underwent abdominal sonography for further diagnostic evaluation (Nos. 4, 8, 14, 15, 17 and 20). Three of them were cats, two ferrets and one dog. Lymph node enlargement was the most common finding (n = 5). Lymphadenopathy of the abdominal lymph nodes was detected with the help of ultrasound in above- mentioned three cats (Nos. 4, 15, 20), one ferret (No. 17) and the dog (No. 14). Two patients showed changes of the intestinal wall, one of them showed a thickened intestinal wall and layer loss (No. 14) and the other showed masses adhering to the intestinal wall (No. 15). Ascites was found in two animals (Nos. 8, 14). The abdominal ultrasound of one ferret showed polycystic kidneys, one cat showed nephropathy (Nos. 8, 4). Splenomegaly and changes of the echogenicity were detected in one patient and another patient had a neoplasia on the spleen (Nos. 4, 8). Hepatopathy was found once and hepatomegaly once (Nos. 8,14). The ultrasound of one ferret showed pancreatic changes, the first suspected diagnosis was an insulinoma (Nos. 8). One patient had mild gastroenteritis (No. 4).

3.5 Cytology

Three out of the five lymph node cytology samples were indicative of mycobacterial infection (Nos. 4, 14 and 17). Monocytes filled with non-stainable or negatively stained rods were found in three cytologic samples (Nos. 4, 17 and 14). Two lymph node cytologies were not indicative of mycobacteriosis, both were suggestive of a reactive state (Nos. 20, 21).

In the cytology of the liver (No. 15), macrophages carrying intracytoplasmic acid-fast rods, were found, which is indicative of a mycobacteriosis infection. The cytology of the jejunal mass did not indicate a mycobacteriosis infection, foamy macrophages and mast cells were observed, but no bacteria with negative staining were found (No. 2). In the cytology of the skin, neutrophils and epithelioid cell macrophages and a few lymphocytes and plasma cells were found, but no pathogen structures (No. 18).

3.6 Necropsy

Lymphadenopathy was observed in eight of the 14 cases where necropsy was performed (Nos. 2, 9, 10, 12, 14, 17, 19 and 22). These cases included four cats, as well as one rabbit, one ferret, one chinchilla, and one dog. In some, only the abdominal (Nos. 9, 12 and 22) or intrathoracic (No. 19) lymph nodes were enlarged, while in others the external (No. 14), intrathoracic (No. 2) or both (Nos. 10 and 17) were enlarged in addition to the abdominal lymph nodes. Lymphadenopathy of these cases was also clinically detected in one cat, one ferret and through abdominal ultrasound in the dog (Nos. 9, 14 and 17). No clinical data were available for the remaining animals, or further diagnostics were not performed.

3.7 Histopathology

In every case, a granulomatous or pyogranulomatous inflammation was detected. The former is characterized by the presence of cells of the mononuclear-phagocytic system (MPS), such as macrophages, multinucleated giant cells, epithelioid cells and, in smaller numbers, lymphocytes, fibroblasts and plasma cells. In pyogranulomatous inflammation, neutrophils are also observed (50).

3.8 Results of PCR and Culture and clinical symptoms

All detected species belong to the NTM. In 17 of 21 PCRs a slow-growing mycobacterial species was identified. These include Mycobacterium xenopi, Mycobacterium genavense, Mycobacterium celatum, and in 14 cases, the mycobacteria of the Mycobacterium avium complex (MAC). In four of these 14 cases, the subspecies could be identified: three times M. avium ssp. hominissuis and once M. avium ssp. avium. Fast-growing mycobacteria species were determined by PCR in two animals. The species were M. fortuitum and both M. smegmatis and M. goodii in another case. M. fortuitum was detected by culture only in another case. Fastidious mycobacteria species were present in two cases, the species were M. lepraemurium and M. tilburgii.

Of the 13 cats, seven were infected with Mycobacteria of the MAC, the subspecies was determined in two of them (M. avium spp. avium, M. avium spp. hominissuis) (Nos. 1, 2, 3, 4, 9, 10 and 11). Disease was disseminated in three of them. Gastrointestinal signs were observed in five cats, respiratory disorders in three cats, other signs noted were lymphadenopathy (n = 3), neurological signs (n = 2), abdominal mass and apathy (n = 2). Other clinical signs noted were jaundice, ocular disorders and dehydration.

Two had an infection with M. fortuitum. One of them had a pyogranulomatous pneumonia (No. 19) and the other a pyogranulomatous lymphadenitis (No. 20).

One cat was infected with M. smegmatis and M. goodii. One month after castration, the cat showed lumps and fistulas on the abdomen, which were removed by two further surgeries. Suture dehiscence occurred as a complication and the tissue had to heal secondarily. The clinical examination also revealed organomegaly (No. 18).

The cat with M. genavense infection showed lymphadenopathy, jaundice, gastrointestinal signs and dehydration (No.15). The cat infected with M. xenopi had a tracheal mass and therefore suffered from respiratory distress (No. 16). The one with M. lepraemurium showed cutaneous lesions on the face (No. 21).

The dog was infected with disseminated M. avium spp. hominissuis and showed gastrointestinal disorders and lymphadenitis (No. 14).

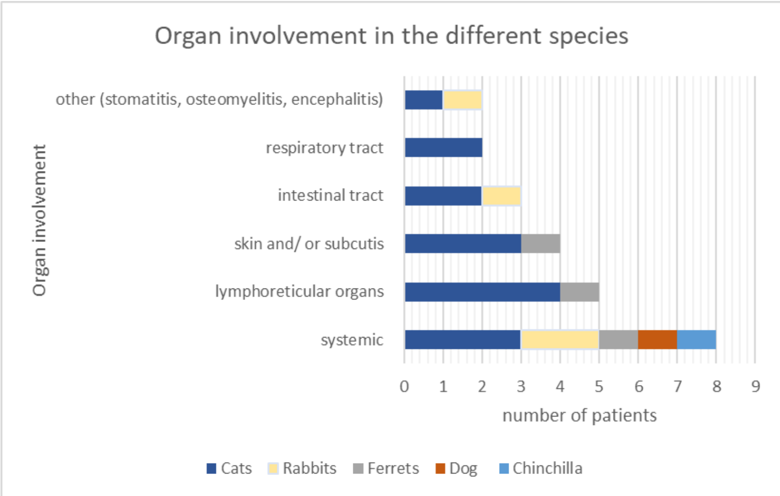
All four rabbits were infected with M. avium, in one of them the subspecies M. avium spp. hominissuis was identified. Two of them had systemic disease. One was lethargic, one had orthopedic disorders, one had neurologic signs as well as hypersalivation, and one had gastrointestinal signs (Nos. 5, 6, 12 and 13).

Two ferrets were infected with M. avium, one showed gastrointestinal signs, neurologic disorders, an abdominal mass, and dehydration (No. 8). The other had a mycobacterial skin infection and it was euthanized two years later due to an abdominal mass, but no necropsy was performed. Thus, a mycobacterial cause of the mass could not be confirmed (No. 7). The ferret with M. celatum had gastrointestinal signs, lymphadenopathy, orthopedic disorders, and fecal incontinence as well as urinary dysfunction (No. 17).

The chinchilla was infected with M. tilburgii. Unfortunately, no clinical data was available (No. 22).

Figure 1

Overview of organ involvement with granulomatous inflammation due to Infection with mycobacteria in the different small animal species



The number of involved organs is higher as the number of affected animals, because in most patients more than one organ was involved. Infestation of more than three organs was classified as systemic.

Table 2

Results of histopathologic examination, organ involvement and identified mycobacterial species in different small animal species.

No.	species	Organs involved	PCR and sequence analysis
1	cat	subcutaneous fat tissue	M. avium spp.
2	cat	intestine, liver, mesenteric- and sternal lymph nodes	M. avium spp.
3	cat	bone, soft tissue	M. avium spp.
4	cat	mesenteric lymph nodes	+ culture: M. avium spp. hominissuis
5	rabbit	caecum, colon	M. avium spp.
6	rabbit	brain	M. avium spp.
7	ferret	skin	M. avium spp.
8	ferret	spleen, lymph nodes	M. avium spp.

9	cat	systemic	+ culture: M. avium spp. avium
10	cat	systemic	M. avium spp.
11	cat	systemic	M. avium spp.
12	rabbit	systemic	+ culture: M. avium spp. hominissuis
13	rabbit	systemic	M. avium spp.
14	dog	systemic	M. avium spp. hominissuis
15	cat	intestines, lymph nodes	M. genavense
16	cat	trachea	M. xenopi
17	ferret	systemic	M. celatum
18	cat	skin, subcutaneous fat tissue	M. smegmatis, M. goodii
19	cat	lungs, pulmonar lymph nodes	Culture (lungs): M. fortuitum
20	cat	lymph nodes	M. fortuitum
21	cat	skin	M.lepraemurium
22	chinchilla	systemic	M. tilburgii

3.9 Therapy

Therapy data were obtained from 15 patients. Most patients received symptomatic therapy, antibiotic treatment and/or glucocorticoids. Patients almost always received a combination therapy of the above-mentioned drugs. Specific therapy against mycobacteriosis, i.e. triple antibiotics, was only started in case No. 4. This cat had a M. avium hominissuis infection that was treated with azithromycin (10 mg/ kg orally once daily, Zithromax®, Pfizer, Vienna, Austria), rifampicin (10 mg/ kg orally twice daily, Rifoldin®, Sanofi- Aventis, Vienna, Austria) and enrofloxacin (5 mg/kg orally once daily, Baytril®, Provet, Wels, Austria). The cat was euthanized after a short time due to deterioration of the clinical condition, as the disease was already advanced (14). The cat with M. fortuitum pneumonia (No. 19) was treated with double antibiosis consisting of Enrofloxacin (Baytril) and Ampicillin and later single antibiosis with clindamycin (23). Four patients were treated with one antibiotic substance, six animals with glucocorticoids. One cat received glucocorticoids because of a gastrointestinal lymphoma, as chemotherapy was stopped due to mycobacteriosis infection

(No. 2). In the other animals the glucocorticoid therapy was administered as anti-inflammatory drug. Ten patients received symptomatic therapy. The cat that achieved remission of signs caused by M. fortuitum infection (No. 20) was treated symptomatically and with antibiotics. In response to an improvement of clinical signs, a specific therapy was discontinued at the owner's request. Two cats were treated surgically, one by removing a mammary gland mass caused by M. avium panniculitis (No. 1), in the other, abdominal nodes and fistulas caused by M. smegmand M. goodii were removed (No. 18). In the second case, suture dehiscence occurred, so the wound had to heal secondarily. The cat was additionally treated with antibiosis, consisting of marbofloxacin for eleven days several times, then double antibiosis with Enrofloxacin (25 mg orally once daily) and Clarithromycin (50 mg orally twice daily) and after that Doxycycline (5 mg/kg orally twice daily). Unfortunately, outcome data were not obtainable in both cases.

3.10 Outcome

In 13 cases the patients were euthanized, two died and one went into remission. In one patient

it could not be determined whether euthanasia or death was involved and in five patients there were no data on the outcome. The patient that went into remission was a cat with mycobacterial lymphadenitis caused by M. fortuitum (No. 20).

4 Discussion

This study describes NTM infections from 13 cats, four rabbits, three ferrets, a dog and a chinchilla from Vienna, Berlin, and New York. According to the clinical examination gastrointestinal signs (n = 12), abdominal masses (n = 5), enlargement of peripheral lymph nodes (n = 4), respiratory signs (n = 4) and dehydration (n = 4) were most frequently detected disorders. In contrast, only two cats and one ferret showed skin alterations, which were observed most frequently in a study of cats with mycobacterial infection in Great Britain (51). It is likely that cutaneous lesions were rarely seen in cats in this study, as most cats were infected with *M. avium* which often leads to systemic disease (1).

Consistent with previous literature, lymphadenomegaly as well as hepato- and splenomegaly were a regular finding on abdominal ultrasound in the cats of the present study (14). In one study internal lymph node involvement was more commonly associated with *M. avium* infections than infections with other mycobacteria (51). These results are comparable to our study, in which lymph node involvement was also found more frequently in animals with M. avium infection. Seven of these 13 animals with lymphadenopathy had an infection with *M. avium*. Probably, this finding is a result of the high incidence of *M. avium*-infections in the animals of the present study.

In accordance with other studies, hematologic alterations including neutrophilia (n = 4), monocytosis (n = 4) and anemia (n = 4) were nonspecific (1, 30). Moreover, thrombocytosis in one cat was probably paraneoplastic due to a lymphoma (No. 2). The blood count of one ferret (No. 8) revealed mild anemia (hematocrit: 31%), while no changes were observed in another ferret (No. 17), consistent with findings reported in other studies (44).

Ziehl-Neelsen staining revealed acid-fast rods in all cases, which led to the suspicion of a mycobacterial infection. However, positive Ziehl-Neelsen stains are not specific for mycobacteriosis, as they can also reveal positive results in the presence of other bacteria such as *Nocardia spp.* (1) . Ziehl-Neelsen staining can lead to false-negative results due to low bacterial load, poor sample quality or improper preparation, such as errors in fixation, staining, or decolorization, and excessive decolorization. Other reasons for false- negative results are technical issues, including insufficient heat during the staining process or the use of expired or improperly stored reagents, and that some non-tuberculous mycobacteria have less acid-fastness (11).

All identified mycobacterial species were classified as non-tuberculous mycobacteria (NTM). This could possibly indicate that infections caused by non-tuberculous mycobacteria are more common in small animals than infections with tuberculous mycobacteria. However, the number of cases is too low to be able to make a statement about the prevalence of the entire population. Nevertheless, case reports of tuberculosis have also been published in cats, dogs, rabbits, and ferrets. In a case report of a ferret with tuberculosis, *M. bovis* was found as the causative species (56). Tuberculosis is rarely reported in rabbits. However, case reports of *M. caprae* and *M. bovis* exist (55). Tuberculous mycobacteria identified in cats include *M. bovis* and *M. microti (17, 51-53)*, while in dogs, case reports primarily document infections with *M. bovis* and *M. tuberculosis* (54). Seventeen of the detected NTM in this study were slow-growing, two fastidious and three rapidly-growing mycobacteria. As with dogs and cats, humans acquire slow-growing NTM infections from the environment, there are no reports of direct transmission from infected animals to humans. Thus, the zoonotic risk seems to be negligible. Usually, a confirmed case of NTM does not need to be reported to the health authorities (1).

With 14 of 22 cases, most of the identified species belonged to the MAC, which corresponds to the results of a study in which representatives of the MAC made up a large proportion of the NTM (51). Mycobacteriosis was disseminated in eight patients. *M. avium* was detected in six of these eight cases, the subspecies *M. avium spp. hominissuis* was determined twice and *M. avium spp. avium* once. Due to the systemic spread, advanced stage of disease and lack of specific treatment, the outcome of these cases was fatal. These results are in accordance with other studies, which have found that disseminated *M. avium* infections usually have a poor prognosis (14, 12, 34, 39, 38 and 41).

The only dog of this study suffered from a systemic *M. avium hominissuis* infection. This dog showed mainly gastrointestinal signs and abdominal ultrasound revealed lymphadenopathy as well as enteropathy. Mycobacteriosis was diagnosed by PCR after FNA from mesenteric lymph nodes and liver. Only a few case reports on dogs infected with *M. avium* subspecies *hominissuis* exist. According to the literature, dogs with disseminated disease were often presented with lymphadenopathy, gastrointestinal signs, weight loss, and fever (34, 57 and 38). Other signs noted were persistent lameness and cutaneous disease (39, 36). A case report of a dog which had been under immunosuppressive therapy and showed a generalized swelling of the tongue and mandibular as well as retropharyngeal lymph nodes was recently published (59). A case report from South Africa describes a dachshund with *M. avium* infection, specifically *M. avium spp. paratuberculosis*. This dog exhibited comparable signs to those in the dachshund-mix of the present study (No. 14), including chronic gastrointestinal disorders and lymphadenopathy. The source of infection was not clearly identified, but sheep in the area had paratuberculosis, so it is reasonable to assume that the dog might have contracted the disease by ingesting infectious sheep feces. Although, this could not be clearly confirmed, the dog had lived in this area for 18 months (58). A study conducting intestinal wall biopsies from 14 healthy dogs and 42 with chronic gastrointestinal signs proved *M. avium spp. paratuberculosis* DNA in 8 of the 42 dogs with chronic gastrointestinal signs (35). These results, along with the case of the dog in the present study, suggest that M. avium infection should be considered as a differential diagnosis in dogs with chronic gastrointestinal signs.

M. celatum that caused systemic mycobacteriosis was detected in a ferret of the present study (No. 17). There are only three case reports of *M. celatum* infections in ferrets, two of which also showed systemic disease and concerned animals were euthanized due to their poor condition (60, 61). In the third ferret splenitis was diagnosed. Clinical signs improved initially after triple antibiotic therapy, but the condition worsened until it died after discontinuation of the therapy (62).

In the chinchilla (No. 22) of the present study, in which a systemic mycobacteriosis was observed, *M. tilburgii* was proven by PCR. To date, there are no case reports of infection with *M. tilburgii* in chinchillas, but *M. genavense* infections involving liver and lungs as well as systemic *M. avium spp. hominissuis* infections are reported in chinchillas (46, 47).

M. lepraemurium, that belongs to fastidious growing mycobacteria, was identified in cat No.

21. In accordance with a few case reports, clinical signs associated with this mycobacterium sp. were cutaneous lesions on the head (63, 64). Nodules located in the periocular area, on the ear-base region, as well as on the ventral aspect of the tongue have also been reported in cats with *M. lepraemurium* infection (65). The outcome in this case was not documented, but the wedge biopsy revealed inflammatory changes that extended to the excision margins. As spontaneous healing is not expected, extensive surgical excision is recommended. However, it is not always possible to guarantee free margins.

One cat with a circumferential enlargement of the mammary gland, which proved to be panniculitis and steatitis caused by *M. avium*, was treated surgically (No. 1). Unfortunately, no outcome data was available, but the prognosis was good as the inflammatory changes did not extend to the margins.

M. fortuitum caused respiratory disease in one cat and lethargy, gastrointestinal signs as well as lymphadenomegaly in another cat (Nos. 19, 20). In contrast, granulomatous panniculitis was mostly reported in case reports of cats with *M. fortuitum* infections according to the literature (67, 24, 21 and 22). Cutaneous signs and panniculitis caused by *M. smegmatis* and *M. goodii* were consistent with findings in the literature (No. 18) (21, 68, 22 and 69). *M. xenopi* caused a tracheal mass in a cat (No. 16), interestingly there is the second case report of a cat with a tracheal mass caused by *M. xenopi* (70). In other case reports of cats, the M. xenopi infection was systemic (19, 71).

M. genavense infection was diagnosed in one cat (No. 15) of this study showing gastrointestinal signs. Pathohistological examination revealed a granulomatous enteritis and lymphadenitis. To the best knowledge of the author, this is the second report of a *M. genavense* infection in a cat. The cat from the other case report showed inappetence, coughing, periocular alopecia and pyrexia (18).

Five of seven cats infected with *M. avium* showed gastrointestinal signs. In several studies, only unspecific signs such as weight loss were observed in cats with *M. avium* infection (30). Unfortunately, weight was not monitored in the cats in this study due to the retrospective nature. In other case reports, *M. avium spp. hominissuis* infections in cats were also disseminated like in cat No. 4 (12, 72, 73). However, signs of disseminated *M. avium* *hominissuis* infections can vary, as other case reports have documented instances with only neurological symptoms or only subcutaneous lesions (73, 74). In one cat with *M. avium* infection, in which the *subspecies avium* was identified (No. 9), it showed a disseminated course of disease, as did a case report of another cat with *M. avium spp. avium* infection (75).

All four rabbits were infected with *M. avium*, one of them was found to have an infection with subspecies *M. avium spp. hominissuis* (Nos. 5, 6, 12, 13). Two of these rabbits developed systemic disease. One rabbit was lethargic, one had orthopedic signs, one had neurologic signs and hypersalivation, and one only had gastrointestinal signs (41). A rabbit from a case report with *M. avium* infection also showed gastrointestinal signs (43). Moreover, *M. avium* was detected in slaughtered asymptomatic rabbits as incidental finding (76).

Five cats were tested for retroviral infection. (Nos. 4, 10, 15, 16, 19). All of them were negative for FeLV and FIV infection. In a study with cats, no correlation of mycobacteriosis with infection with FIV and FeLV was found either, as only 2 out of 72 cats tested were FIV-positive (51).

Six out of 13 cats of the present study were European shorthair cats (Nos. 1, 2, 4, 10, 15, 19). The high incidence of mycobacterial infections in ESH cats is likely due to their frequent occurrence in many cat populations. Among the 13 cats, one was a Siamese mix, and one was an Abyssinian cat (11, 16). Two studies indicate a possible predisposition of Siamese and Abyssinian breeds to mycobacterial infection (30, 77). No sex predisposition was found in this for any animal species, even though a study about cats found a male sex predisposition (51). Since mycobacterial infection was detected in six indoor-only cats, it should also be considered as a potential differential diagnosis in similar cases. However, it was unknown whether they had previous outdoor exposure or where they lived before their current environment. Transmission or source of infection in outdoor animals was probably oral ingestion or skin injury, and in indoor cats through inapparent infection in youth or infection from polluted water or food.

The outcome for the cases included in this study was poor, with 16 out of 17 individuals, for whom data were available, being either euthanized or having died. The reasons for the poor outcome include the fact that the disease was usually diagnosed in a progressive stage or ultimately on post-mortem examination. Therefore, no specific therapy was started and in eight cases it had already spread systemically, which worsened the prognosis (14). Although, the prognosis for disseminated *M. avium* infections is generally poor, successful treatment of affected cats with double or triple antibiotics has been described in case reports (72, 30, 78). In some of the cases reported here, suboptimal therapy with glucocorticoids might have led to progression of the disease.

The main limitation of this study was its retrospective nature, which resulted in incomplete data from the analyzed medical records.

5 Conclusion

This work makes it clear, that infection with mycobacteria should be considered as a differential diagnosis in small animals. Despite typical disease conditions like cutaneous lesions or recurrent gastrointestinal, respiratory signs as well as palpable abdominal masses, and lymphadenopathy, clinical manifestation might be unspecific. Differential diagnoses vary depending on the clinical appearance; in the case of skin involvement, nocardiosis, actinomycosis, fungal and foreign body granulomas, eosinophilic granuloma, abscesses, and neoplasms must be considered as possible differentials. However, also more common diseases like FIP must be excluded in cats with pyogranulomatous lesions. When FNA reveals signs of (pyo-)granulomatous inflammation, an acid-fast staining should be performed in a timely manner. Like in humans, small animals most probably become infected with slow-growing NTM through the environment; direct transmission from animals to humans has not yet been described. However, since the clinical picture is similar to tuberculosis, precautionary measures, such as wearing gloves and a face mask should be taken even in suspicious cases (1). Nevertheless, caution should be exercised with wounds from dog or cat bites, as there are case reports of fast-growing mycobacteria causing skin infections in humans following traumatic injuries from such bites (79, 80).

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