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Case Report

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First report of *Mycobacteria avium* complex (*Mycobacteria intracellulare*) in a cat from Southeast Asia

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Abstract

Case summary A 3-year-old castrated male domestic shorthaired cat, with indoor–outdoor access, was presented for chronic, progressive multinodular to generalised subcutaneous nodules covering much of its body. Previous medical treatment with doxycycline had been unhelpful. Fine-needle aspiration of the nodules revealed intra- and extracellular multibacillary negative staining rods in pyogranulomatous inflammation. Bacterial culture and susceptibility studies isolated *Mycobacterium intracellulare*, with zimine as the drug of choice for treatment. Initial triple therapy with rifampicin, azithromycin and pradofloxacin was ineffective, and was changed to triple therapy with clofazimine, clarithromycin and doxycycline once drug susceptibility was known, which was given for 3 months, after which long-term therapy with clofazimine and clarithromycin was continued.

Relevance and novel information Slow growing *M intracellulare*, a member of the *Mycobacterium avium* complex (MAC), has never been reported to cause disease in cats from Singapore and, by extension, Southeast Asia. The infection in this patient resulted in subcutaneous nodules, which started on the face, then spread to the feet and much of the rest of its body. This is in contrast to that commonly reported for infection with *M avium*, which is also a member of MAC, and may not only present with similar signs in cats, but also progress to systemic spread. Susceptibility studies suggest clofazimine as the drug of choice when treating this infection, and this case supports its use as empirical therapy for veterinarians treating this disease in this region while awaiting culture and sensitivity results.

Keywords: *Mycobacterium intracellulare*; Singapore; Southeast Asia, clofazimine

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Introduction

Mycobacterium avium complex (MAC) consists of multiple non-tuberculous mycobacterial species (NTM), which cannot be distinguished using specialist culture and require genetic testing. As opportunistic saprophytes, the NTM consists of slow-growing and rapid-growing species (RGM) that can cause infections in cats, typically involving skin and subcutaneous tissues (either focal, multifocal or diffuse lesions), but rarely progress to cause systemic disease, except for MAC infections.[1,2] MAC currently consists of *M avium*, *Mycobacterium intracellulare*, *Mycobacterium paraintracellulare* and *Mycobacterium chimaera*.[3,4] *M avium*, *M intracellulare* and *M paraintracellulare* are commonly associated with infection of the respiratory system in human patients, while *M chimaera* has been associated with opportunistic infection during open heart surgery.[3]

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In cats, NTM infections cause cutaneous/subcutaneous nodules or granulomatous panniculitis with variable lymph node involvement. Systemic mycobacteriosis caused by NTM species is rare, other than with *M avium*.[5] Infected cats have typically had a history of outdoor access, with hunting and fighting (contact with infected prey or soil) as predisposing factors for skin damage and secondary mycobacterial infection. This case report describes a case of mycobacteriosis in an immunocompetent cat with *M intracellulare*, presenting with generalised cutaneous and subcutaneous nodules, and no systemic spread.

Case description

A 3-year-old castrated male domestic shorthaired cat, weighing 3.7 kg, was presented to a referral hospital for the evaluation of generalised subcutaneous granulomatous lesions, with occasional bouts of anorexia, pyrexia and diarrhoea. The cat was from a multi-cat household, with an indoor–outdoor lifestyle, with close contact with one other cat plus the owner; however, none had developed similar skin lesions. Skin lesions developed 8 months prior to presentation, beginning on the lips and chin, then spreading gradually to cover most of the body. Eight weeks prior to presentation, a veterinarian had examined the cat's swollen left stifle, including arthroscopically (for which there was no report), and prescribed doxycycline (5 mg/kg PO).

On physical examination, the cat had a body condition score of 4/9 with ulcerative nodules affecting its face and paws (Figures 1 and 2). Serum biochemistry profile with complete blood cell count was unremarkable, other than hyperglobulinaemia. Feline leukaemia virus antigen and feline immunodeficiency virus antibody serology were negative by ELISA. Romanowsky-type (Diff-Quik; Siemens) staining of fine-needle aspirates from nodules yielded intra- and extracellular, multibacillary negative staining rods in pyogranulomatous inflammation, highly suggestive of *Mycobacteria* species. Local health authorities were notified. Mycobacteriosis in a non-food-producing animal is not a notifiable disease and may be treated. Samples were sent for mycobacterial culture, speciation and susceptibility testing at the National Jewish Health Advanced Diagnostic Laboratories (Denver, CO, USA). Thoracic radiographs were taken with no significant abnormalities observed.

The cat was empirically treated with triple therapy antibiotics (azithromycin [Zithromax; Pfizer] 5.5 mg/kg PO q24h, marbofloxacin [Marbocare Animalcare] 5.5 mg/kg PO q24h and rifampicin [Royce Rifampicin; Royce Pharma Manufacturing] 10 mg/kg PO q24h). Marbofloxacin was substituted with pradofloxacin (Veraflox; Bayer Animal Health GmbH) at 8 mg/kg PO q24h after 4 weeks due to lack of clinical improvement. At week 5, bacterial culture were

Figure 1 The 3-year-old castrated male cat on initial presentation, with multinodular to generalised subcutaneous swelling, beginning on the face extending to the chest, flanks and tail base

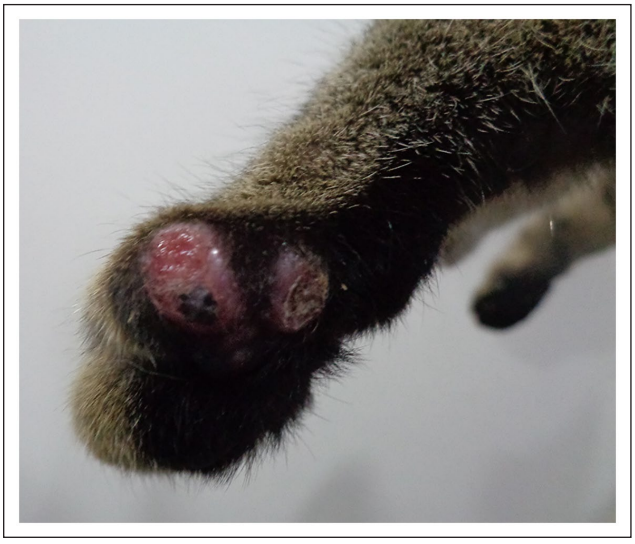

Figure 2 On initial presentation, there were ulcerated nodules on the distal paws

isolated *M intracellulare* using rpoB gene sequencing. Susceptibility studies returned at week 9 (amikacin, linezolid, streptomycin [32 µg/ml], ciprofloxacin, minocycline [>8 µg/ml], rifampicin, doxycycline, moxifloxacin [>4 µg/ml], clarithromycin [2 µg/ml], rifabutin [1 µg/ml], clofazimine [0.06 µg/ml] and trimethoprim/sulfamethoxazole [4/76 µg/ml]) suggested clofazimine as the drug of choice. During triple therapy, the cat's condition deteriorated, and its body weight dropped to 3.4 kg (a loss of 10% of its body weight), assumed to result from chronic diarrhoea that was predominantly a side effect of the triple therapy (Figures 3 and 4). Therapy was changed to clarithromycin (Klerimed;

Figure 3 After 11 weeks of triple therapy with azithromycin, rifampicin and pradofloxacin, the cutaneous lesions had progressed, with formation of new lesions and pre-existing nodules growing progressively larger. The cat had chronic diarrhoea and had lost 10% of its body weight

Figure 4 At week 11 after the initiation of triple therapy, new lesions emerged and ulcerative nodules were seen predominantly on the distal paws

Figure 5 After 8 months of therapy with clofazimine plus clarithromycin, the patient's weight had stabilised at 4.8 kg and quality of life was much improved. There was marked reduction in skin erythema, erosion and ulceration, with overall regression of the size of the nodules

Figure 6 After 8 months of therapy with clofazimine and clarithromycin, there were still persistence of infection at all digits, manifested as mild swelling and erythema

Medochemie) 20 mg/kg PO q12h, clofazimine (Lamprene Novartis Pharmaceuticals) 50 mg/cat PO q48h and doxycycline (Doxyvet 100; AHM) at 8 mg/kg PO q24h. After 4 weeks of the new triple therapy, the cat's weight returned to 3.7 kg (a 10% increase in body weight), with no new lesions, and slow regression of the subcutaneous soft tissue swellings but nodules persisted on the face, pinnae and paws. At the most recent review, 8 months after the initiation of clofazimine and clarithromycin, the cat's weight stabilised at 4.8 kg (an increase of approximately 30% of its body weight from its lowest weight) and serum globulin and ionised calcium concentrations were within normal reference intervals (Figure 5 and 6). There was persistence of lesions affecting the cooler anatomical regions (ear pinnae, face and paws) with mycobacteria observed in lesser quantities from earlier fine-needle aspiration samples. No further attempts were made to re-culture, and drug dosages were re-adjusted to reflect the cat's current body weight.

Discussion

This is the first case of the slow growing NTM, *M intracellulare*, causing disease in a cat being reported from Singapore and, by extension, Southeast Asia. Being ubiquitous in the environment, the bacterium most likely established infection in the gastrointestinal tract, which caused chronic diarrhoea before systemic spread. In patients with human immunodeficiency virus, the incidence of disseminated MAC disease is 20–40% in people with HIV with advanced immunosuppression and/or a CD4 count <50 cells/mm.[3,4] Localised granulomatous lesions are most often due to direct inoculation of the infection under the subcutis that do not

typically spread systematically.[5] In the present case, the primary cause of immunosuppression that led to systemic spread was unable to be ascertained. *M intracellulare* has rarely been reported to cause disease in cats. In one case report, a 4-year-old female Persian cat in Germany was presented with a history of anorexia, chronic weight loss and depression, but no cutaneous lesions.[6] On examination, that cat showed weakness, emaciation and marked dehydration. Radiography revealed an abdominal mass, measuring approximately 3–5 cm in diameter. Given the poor prognosis and because treatment could not be afforded, the cat was euthanased. Necropsy revealed generalised lymphadenopathy (peripheral and internal lymph nodes were approximately 3–4 times their normal size) and histopathology revealed severe multifocal to diffuse granulomatous inflammation of lymph nodes, spleen, lung, liver, intestine and bone marrow.[6]

In the present case, the signalment and manifestation was more consistent with a single case reported from the UK, which also had no systemic signs.[7] In that case, it was noted that neutered domestic short-/long-haired male cats are predisposed to MAC infection, which typically presents with lumps (which may or may not be ulcerated with exudative discharge) not only found primarily on the head, but also occuring all over the body.[7] This may be attributed to the organisms' thermal preference to grow at 31.5°C, which is manifested clinically as lesions tend to persist on cooler regions of the body, such as the face, ear pinnae and paw pads, as seen in the present case.[8] This is in contrast to *M avium* infections that have a breed predisposition to Abyssinian and Somali cats, with the most consistent physical findings being slow disease progression, chronic weight loss and ill-thrift. Systemic involvement is common, with thoracic radiographs demonstrating a distinctive severe diffuse interstitial pattern, despite the cats showing pulmonary signs.[9]

Clinically, the cat in the present report perhaps most closely resembles a case of feline leprosy, caused by *Mycobacterium lepraemurium* and several other mycobacteria, characterised by rapidly progressive, locally spreading, non-painful, raised, fleshy, cutaneous and subcutaneous nodules, with larger lesions tending to ulcerate with no internal dissemination to internal organs.[10] Recently, the complete genome sequencing of *M lepraemurium* suggested that it might actually be more related to MAC, which may partially explain this observation in our case.[11] The drugs commonly used in the treatment of MAC infections are macrolides (eg, azithromycin, clarithromycin), clofazimine, rifampicin and fluoroquinolones (eg, pradofloxacin, moxifloxacin).[12] Tetracyclines (eg, doxycycline) are not commonly reported to be effective in MAC infections, with the current case being an exception.[13] In the present case, empirical treatment with triple therapy caused diarrhoea and weight loss, most likely due to rifampicin and/or azithromycin.[12] There is always concern over the use of these drug combinations because marbofloxacin and pradofloxacin are second-line antibiotics and clarithromycin, azithromycin and rifampicin are third-line antibiotics, and it has been suggested that rifampicin should be for use in people only.[14] Although the use of triple therapy is needed to reduce the risk of drug resistance, the risk of generating resistant clones remains because compliance is hard to maintain when a cat has to be given three drugs every day for many weeks.

Based on susceptibility results, treatment was amended to clofazimine, clarithromycin and doxycycline for 3 months, before long-term therapy was continued with clofazimine and clarithromycin. Doxycycline in its tablet form was discontinued due to the risk of drug-related oesophagitis and stricture formation, with no relapse after its withdrawal. Clofazimine is a phenazine dye that accumulates in large concentrations within macrophages where it promotes the production of oxygen-derived free radicals. When given orally, it is absorbed variably, distributed unevenly throughout the body, concentrating in the liver, spleen, lung, adipose tissue and skin, and can cause hepatotoxicity.[15] Owing to the increased incidence of drug-resistant tuberculosis (TB), the World Health Organization has suggested that the use of second-line TB medication such as clofazimine should be restricted.[16] In the present case, the medication was made available only with a prescription. Ethambutol is another first-line TB medicine that may be added to longer multidrug-resistant TB regimens. At recommended dosages, ethambutol is safe with demonstrated susceptibility in cats.[17] Clarithromycin, a macrolide antibiotic, is effective in singular use or in combination with other drugs for the treatment of MAC infections.[18] Serum ionised calcium concentration should ideally have been part of the routine assessment and monitoring of mycobacterial infections because hypercalcaemia is commonly associated with an underlying granulomatous disease process.[19] In addition, this was not regularly assessed with full abdominal ultrasound due to the lack of experience in managing this disease.

To guide therapy, it is important to know which mycobacteria are most likely to cause disease in cats in any country. For example, in the UK, *Mycobacterium microti* (a cause of tuberculosis) is the most common mycobacterial infection in cats, and so empirical triple therapy, as initially selected in the current case, would be a sensible first choice. However, in Australia, *Mycobacterium smegmatis* and *Mycobacterium fortuitum* are most common, and so the best first choices are fluoroquinolones and doxycycline, whereas, in America, *M fortuitum* and *Mycobacterium chelonae-abscessus* are seen most frequently, and so clarithromycin is a good first choice, and older fluoroquinolones (eg, marbofloxacin and enrofloxacin) should be avoided.[20,21] Inexperience of treating these cases meant a

very high dose of pradofloxacin was chosen; it should have been 5 mg/kg q24h PO.

Conclusions

This report describes a case of mycobacteriosis caused by *M intracellulare* in a cat that developed extensive cutaneous and subcutaneous lesions, but no systemic infection such as *M lepraemurium*. Clofazimine should be prescribed empirically for this disease in this region as part of a triple therapy with doxycycline and clarithromycin.

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Ethical approval The work described in this manuscript involved the use of non-experimental (owned or unowned) animals. Established internationally recognised high standards ('best practice') of veterinary clinical care for the individual patient were always followed and/or this work involved the use of cadavers. Ethical approval from a committee was therefore not specifically required for publication in *JFMS Open Reports*. Although not required, where ethical approval was still obtained it is stated in the manuscript.

Informed consent Informed consent (verbal or written) was obtained from the owner or legal custodian of all animal(s) described in this work (experimental or non-experimental animals, including cadavers) for all procedure(s) undertaken (prospective or retrospective studies). No animals or people are identifiable within this publication, and therefore additional informed consent for publication was not required.

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