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REVIEW

Resolution of feline *Mycobacterium* panniculitis despite protracted treatment with methylprednisolone acetate

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Saprophytic or non-tuberculous mycobacteria are ubiquitous in the environment. They can cause opportunistic infections when the skin is broken and typically manifest with draining sinus tracts or cutaneous nodules. This report details the first confirmed *Mycobacterium smegmatis* panniculitis in a cat in South Africa. Despite repeated treatment with methylprednisolone acetate for six months prior to diagnosis, the cat made an uneventful recovery once switched to doxycycline and marbofloxacin.

Keywords: *Mycobacterium smegmatis*, non-tuberculous mycobacteria, cat, sinus tract, steroids, doxycycline, marbofloxacin, culture, PCR, cytology, pepper pot

Introduction

There are in excess of 170 mycobacterial species (Fedrizzi et al. 2017). Some, most notably *Mycobacterium tuberculosis* and *M. bovis*, are obligate pathogens and may even be highly adapted to a specific host species (Van Helden et al. 2009). Obligate pathogens like *M. tuberculosis* tend to be slow growing (taking up to eight weeks to grow in culture) and tend to produce tubercles – granuloma characterised by central caseous necrosis that play an important role in mycobacterium transmission (Ehlers & Schaible 2012). Saprophytic mycobacteria are ubiquitous in soil and water but cause opportunistic infections when introduced through a skin defect. They usually grow more rapidly than the obligate pathogens in cultures (within 3–10 days) and are much more likely to manifest as draining sinus tracts (Miller et al. .2013a). Other species form granulomata, may present with lymphadenopathy, systemic infections or panniculitis (Malik et al. 2009; Malik et al. 2000; Munro et al. 2021; O'Brien et al. 2017). Specific disease manifestations are associated with particular mycobacterial species and clades, but as more species are discovered and studied, these distinguishing features are becoming more blurred (Van Helden et al. 2009). Recently, awareness of the effect of host genetics and immunity in determining disease phenotype has increased and saprophytic or non-tuberculous mycobacteria (NTM) are emerging as important systemic pathogens in specific populations, particularly in immunosuppressed hosts (Baral et al. 2006; Novick et al. 1990; Ratnatunga et al. 2020; Van Helden et al. 2009). Specifically, methylprednisolone has been shown to enhance lesions in experimentally infected rabbits (Paschal et al. 1992).

Patient presentation

A ten-year-old 4.5 kg neutered male domestic shorthaired cat initially presented with a discharging skin defect suspected to be cat fight abscess that had burst. He was treated symptomatically with local cleaning, cefovecin (two treatments 14 days apart, dose not specified, Convenia, Zoetis) then with enrofloxacin (5.55 mg/kg sid for 10 days, Baytril, Elanco). Although the skin defects healed at times, the skin remained thickened and inelastic. When draining sinuses appeared for the third time at the same site five months after initial presentation, the problem was investigated. A biochemistry screen was unremarkable bar a hyperglobulinaemia of 56 g/l and a benchtop test failed to detect FeLV or FIV. Bacterial culture of skin biopsies yielded *Staph. pseudintermedius* sensitive to all antibiotics tested. Histopathology revealed pyo-granulomatous inflammation. H&E, PAS and ZN stains failed to identify causative organisms, so sterile granuloma syndrome was suspected. Methylprednisolone acetate (18–20 mg/dose; DepoMedrol, Zoetis 40 mg/ml) was injected subcutaneously ten times over six months, with 13–27 days between injections as the owner felt unable to administer oral medication. Initially, the lesions appeared to improve. Old lesions healed, but when new ones developed further cranially and seemed to be associated with some pain, limiting mobility, referral was initiated. Weight had remained unchanged throughout and the owner noted no systemic changes, specifically no increased water intake.

Clinical examination revealed no systemic abnormalities. There were punched out 3–5 mm skin defects along the dorsum from the lumbosacral junction to the caudal thoracic area that oozed serous discharge. This had occasionally been more purulent according to the owner. Between the defects, there were slightly raised areas of skin 1–2 cm in diameter that felt subtly fluctuant, suggestive of fluid accumulations below the skin.

Lastly, there was a firm 3 cm deep, 3–4 cm long subcutaneous swelling in the R inguinal area (Figure 1). There were tiny red, slightly sunken defects in the overlying skin with mild erythema with one full-thickness skin defect further caudally. Aspiration appeared painful.

Cytology revealed large numbers of well-preserved neutrophils with lower numbers of active macrophages in a background of erythrocytes. No infectious organisms were evident on Diff-Quick stained smears. Serum glucose concentration, packed cell volume and blood smear were unremarkable. Punch biopsies for culture were collected from intact skin in fluctuant areas along the back and from the inguinal lesion after preparing the skin as if for surgery, making sure to include as much subcuticular fat as possible. Colonies suspicious of mycobacteria became evident nine days after inoculation into blood agar and mycobacteria

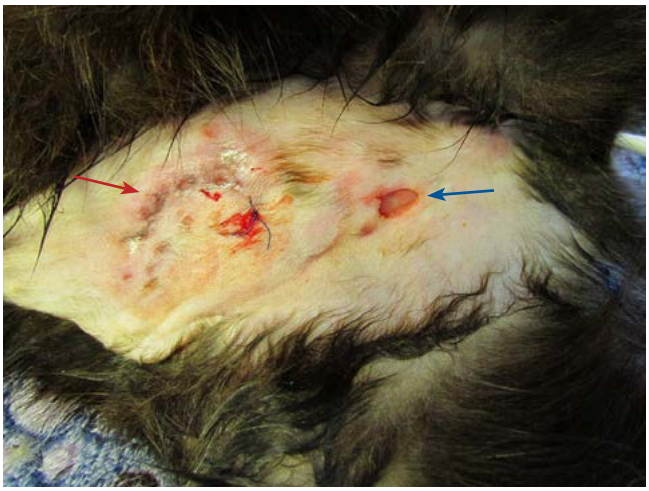

Figure 1: Inguinal biopsy site (head is to the left)
Red arrow: 'pepper pot' lesions thought to be suggestive of infection with NTM in cats (Greene et al. 2012). Blue arrow: full-thickness defect, not a biopsy site

were confirmed on day 12. Disc diffusion suggested doxycycline, fluoroquinolones, aminoglycosides, potentiated sulphas and chloramphenicol could be considered for treatment. PCR performed by a specialist mycobacterial laboratory[a] identified the species as *M. smegmatis*.

Management and outcome

The owner received training on how to administer tablets. The cat was discharged on 5 mg prednisolone once daily and 0.05–0.1 mg buprenorphine twice daily to ease discomfort, pending culture results. Lesions remained static. Once the sensitivity results were known, he was changed to 50 mg doxycycline (11.1 mg/kg) with 12.5 mg marbofloxacin (2.78 mg/kg), both once daily. Six weeks into treatment, the cat presented vomiting with apparent discomfort swallowing. Skin lesions were already much improved. Oesophagitis was suspected, managed with omeprazole, sucralfate and maropitant and resolved uneventfully. Two months after the onset of treatment, skin lesions had reportedly resolved completely, and appetite and habitus were normal. Treatment continues at the time of writing.

Discussion

This is the first reported case of infection with a saprophytic mycobacterium in a domestic cat in South Africa. The bacteriologist involved with this case reportedly isolates approximately one saprophytic mycobacterium every two months, most commonly from poorly healing wounds in cats, more rarely from dogs (Dr M Henton, Vetdiagnostix, personal communication); 37 different NTM species were isolated from wildlife over 12 years by the tuberculosis laboratory at the Onderstepoort Veterinary Institute (Gcebe & Hlokwe 2017), and NTM infections are regularly diagnosed in gold miners (Van Halsema et al. 2015), so infections with NTM appear underreported rather than exceptionally rare in South Africa.

Diagnosis of NTM infection requires a high index of suspicion in either the attending clinician or the bacteriologist, ideally both. Although initial lesions may resemble cat bite abscesses (as they did in this case), discharge is not usually malodorous and healing is incomplete (Malik et al. 2000). The inguinal fat pad is a predilection site for NTM infection (Greene et al. 2012; Malik et al. 2000; Miller et al. 2013a). If a cytological sample is collected through intact skin avoiding contaminants, the absence of intracytoplasmic bacteria should increase the index of suspicion for underlying NTM. An alert cytologist may then search for macrophages where mycobacteria, which do not stain with Romanowsky-type stains, can often be observed as negatively staining phagocytosed rods (Malik et al. 2009). Many commercial bacteriology laboratories only culture for 1–2 days unless specifically alerted to the fact that there is clinical suspicion of a slower growing organism. In addition, normal skin flora overwhelm the slower growing mycobacteria in standard skin biopsies as they did in this cat's first culture. If mycobacteria are suspected, normal commensals need to be avoided. This can be achieved by collecting fine-needle aspirates from pockets of exudate under intact skin, by preparing the site surgically prior to collecting biopsies from the subcuticular fat, as was done here (Malik et al. 2000), or by treating the sample with disinfectants like 4% sodium hydroxide that kill commensals but spare mycobacteria (Greene et al. 2012).

There is no single best diagnostic test that identifies or eliminates all mycobacteria: many species, e.g. *M. smegmatis* are readily cultured on blood agar, others require specialised media or conditions while some, e.g. *M. lepraemurium,* are virtually impossible to grow (Lagier et al. 2015). Some appear in large numbers in cytology preparations, others are not detectable. PCR is quicker than culture, and identifies the species in question but is not perfectly sensitive (Greene et al. 2012; Park et al. 2013), and should thus not be used to exclude infection in cases where organisms are not visible on cytology or histopathology.

At referral presentation, the main differentials were of cutaneous sterile granuloma/pyogranuloma syndrome that was poorly responsive/insufficiently immunosuppressed or of a NTM that was present in numbers too low to detect in histopath sections, even with appropriate staining. The few reports of the former rare condition describe cutaneous plaques and nodules rather than draining sinus tracts in affected cats (Giuliano et al. 2020; Miller et al. 2013c). The immunosuppressive dose of oral prednisolone is 4.4 mg/kg/day (Miller et al. 2013b). According to licensing information, the suggested feline dose of methylprednisolone acetate is 1–2 mg/kg repeated once weekly or as needed but an immunosuppressive dose is not specified. Anti-inflammatory doses of 10–20 mg/cat every one to three weeks appear commonly in use (Kuehn 2018). The duration of clinical effect of a single injection is thought to vary between one to more than four weeks (Miller et al. 2013b). When methylprednisolone acetate was used to induce immunosuppression in cats experimentally, 10–20 mg/kg was given at weekly intervals (Novacco et al. 2011; Scorza et al. 2006). Thus doses used in this cat were probably

[a]: DSI-NRF Centre of Excellence for Biomedical Tuberculosis Research; SAMRC Centre for Biomedical Tuberculosis Research, Division of Molecular Biology and Human Genetics; Faculty of Medicine and Health Sciences, Stellenbosch University; Dr WJ Goosen, wjgoosen@sun.ac.za

anti-inflammatory rather than immunosuppressive. The lower dose and the mycobacterial species involved likely explain why clinical signs did not worsen dramatically and bacteria did not disseminate systemically (Greene et al. 2012).

As far as could be determined, this is the first report of an infected cat being treated successfully with marbofloxacin. Enrofloxacin, the only other fluoroquinolone licensed for veterinary use in South Africa, has been associated with retinopathies in cats (Messias et al. 2008) and was avoided for this reason. Most other fluoroquinolones have been used to treat NTM in cats (Malik et al. 2013; Malik et al. 2000), so there was no reason to doubt marbofloxacin's efficacy.

Conclusion

Infections with saprophytic mycobacteria are likely under-diagnosed rather than exceptionally rare in South Africa. The bacteria are difficult to find and grow, so they will readily be missed if not specifically sought. The knowledge that repeated steroid treatment did not lead to systemic dissemination or a dramatic local spread at least in one case has some practical use in ranking differentials for new cases – especially as a clinical trial to assess this issue is unlikely to gain ethics approval. The mycobacterial laboratory that performed the targeted PCR amplicon sequencing in this case is keen to establish a biobank of mycobacteria isolated from dogs and cats in South Africa. Confirmation of the species involved in clinical cases would help determine zoonotic risk to associated humans.

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