CUTANEOUS MYCOBACTERIOSIS IN DOGS AND CATS: A REVIEW

MICOBACTERIOSIS EN PERROS Y GATOS: REVISIÓN DE LITERATURA

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ABSTRACT

Mycobacteria are aerobic, rod-shaped, Gram-positive bacteria belonging to the genus *Mycobacterium*, comprising a wide variety of species distributed worldwide and classified in three different groups: obligate pathogens, facultative pathogens and environmental saprophytes. Facultative pathogens may cause opportunistic infections, called mycobacteriosis. The dermal syndromes caused by mycobacteria in dogs and cats include canine leproid granuloma, feline leprosy and panniculitis The causative specie is different among them, and they have also important differences regarding geographical distribution, clinical features, diagnostic aspects and response to treatment. Clinically, these infections have in common the presence of single or multiple dermal and subcutaneous nodular lesions that may be ulcerated or fistulized. Mycobacteriosis must be considered as a differential diagnosis in every patient with compatible clinical aspects. Treatment recommendations include antimicrobial agents, combined or not, with surgical resection. Considering that some mycobacteria species have significant zoonotic potential resulting in cutaneous lesions clinically indistinguishable from those caused by non-zoonotic organisms, the causative agent involved should be identified whenever possible.

Key words: Mycobacteriosis, Canine leproid granuloma, Feline leprosy, Mycobacterial panniculitis.

RESUMEN

Las micobacterias son bacterias aeróbicas, en forma de bacilo, gram-positivas, pertenecientes al género Mycobacterium, el cual compromete una amplia variedad de especies distribuidas a nivel mundial, las cuales se clasifican en tres grupos diferentes: patógenos obligados, patógenos facultativos y saprófitos ambientales. Los patógenos facultativos pueden causar infecciones oportunistas, denominadas micobacteriosis. Los síndromes dérmicos causados por micobacterias en perros y gatos incluyen el granuloma leproide canino, la lepra felina y la paniculitis. La especie involucrada es diferente entre estos, presentando discrepancias importantes en cuanto a su distribución geográfica, aspectos clínicos y diagnósticos y respuesta al tratamiento. Clínicamente, estas infecciones tienen en común la presencia de lesiones nodulares únicas o múltiples, cutáneas o subcutáneas, que pueden ulcerarse o fistularse. La micobacteriosis debe ser considerada como un diagnóstico diferencial en cada paciente con signos clínicos compatibles. Las recomendaciones de tratamiento incluyen agentes antimicrobianos, combinados o no, con resección quirúrgica. Considerando que algunas especies de micobacterias poseen un potencial zoonótico significativo que resultan en lesiones cutáneas clínicamente indistinguibles de aquellas causadas por organismos no zoonóticos, el agente etiológico debe ser identificado siempre que sea posible.

Palabras clave: Micobacteriosis, granuloma leproide canino, lepra felina, paniculitis por micobacterias

INTRODUCTION

Mycobacteria are aerobic, rod-shaped, Gram-positive bacteria belonging to the phylum *Actinobacteria*, order *Actinomycetales* and genus *Mycobacterium*[1]. The genus comprises a wide-variety of species characterized by a thick cell wall rich in long-chain fatty acids, mostly mycolic acid, which are responsible for their alcohol-acid-resistance feature and contributes to adaptative mechanisms such as aerosolization, surface adherence, phagocytosis resistance, biofilm formation and antibiotic/disinfectant resistance (1,2,3).

More than 150 *Mycobacterium* species have been recognized and due to recent advances in genetic sequencing, among others molecular techniques, new species can be identified more precisely (3,4). These species have been classified in three different groups: obligate pathogens, facultative pathogens, and environmental saprophytes. Host affinity and pathogenic potential are extremely heterogeneous among infective species (5).

The obligate pathogens group include species of the *Mycobacterium tuberculosis* complex, such as *M. tuberculosis, M. bovis* and *M. microti,* that causes tuberculosis in humans and different animal species. These organisms are not able to multiply outside vertebrate hosts and shows a marked host predilection (1,5). *M. tuberculosis* is the primary cause of tuberculosis in humans. It can affect dogs after prolonged close contact with infected people (6), and is considered very rare in cats, probably because this species is naturally resistant (7). Tuberculosis in cats is mostly caused by *M. microti* or *M. bovis,* and they can get infected through rodent hunting or by eating contaminated raw food (7,8).

Facultative pathogens are non-tuberculous mycobacteria that causes opportunistic infections, called mycobacteriosis (9). These microorganisms are ubiquitous and adapted to different niches including water bodies and soil. Over 60 species are known to be opportunistic pathogenic to humans and animals, and there may be geographical differences regarding species prevalence (10).

Non-tuberculous mycobacteria are usually divided into two groups, based on their rates of growth: rapid-growing mycobacteria, which requires about 7 days or less to form colonies, and slow-growing mycobacteria, which take up weeks or months to form colonies in-vitro. There is another group of non-tuberculous mycobacteria species that cannot be cultured using standard methods (1,5,7,9).

Infections by non-tuberculous mycobacteria can cause different clinical manifestation in dogs and cats, evolving the skin, respiratory tract, gastrointestinal system and can even induce disseminated disease (1). Regarding the skin, they can produce granuloma in the cutis and subcutis. Rapid and slow-growing mycobacteria can cause panniculitis syndromes in dogs and cats, although rapid-growing species are more commonly evolved in these cases. Canine leproid granulomas may be caused by slow-growing mycobacteria. Feline lep-

rosy, for its part, is caused by those non-culturable mycobacteria species (5,7). The differences, both in terms of clinical and etiological aspects, between these clinical forms, is very subtle and can be sometimes confusing.

The aim of this article is to review the dermal syndromes caused by non-tuberculous mycobacteria in dogs and cats, such as canine leproid granuloma, feline leprosy and panniculitis caused by non-tuberculous mycobacteria species. Tuberculosis in small animals is usually associated with systemic disease and, despite also affect the skin, this is not the main feature of these infections (6,7,8). For this reason, this group of disease is not in the scope of this review.

EPIDEMIOLOGY AND PATHOGENESIS

Canine leproid granuloma

Canine leproid granuloma (CLG) was first described in 1973, in Zimbabwe, Africa. The disease is commonly diagnosed in countries with climatic similarities, such as Australia, New Zealand, Brazil (11,12) and several states of USA such as California and Florida (13). The etiological agent is still not fully characterized. The growth requirements of the organism remain unknown, and, for that reason, it is not possible to culture it *in vitro* so far (14). Molecular investigation identifies species closely linked to *Mycobacterium simiae* group, which is composed by slow-growing saprophytic bacteria (14,15).

It is speculated that the mode of transmission of the agent is via insect bite. The disease predilection for short-coated large breeds dogs (boxer, rottweiler, foxhound, doberman pinchers) that live predominantly outdoors and lesions occurring at sites more susceptible to insect bites, such as dorsal fold of the ears and the head, support this theory (12,14). Another possible mode of transmission is through traumatic wounds in contaminated environment. A case report of multiple CGL in foxhound dogs domiciled in the same kennels observed infection only in animals involved in hunting activities, but not in those inactive dogs living in close contact, suggesting a traumatic inoculation with contaminated soil and plants (11).

Feline Leprosy

Feline leprosy is caused by a heterogeneous group of fastidious mycobacterial species that generally cannot be cultured using routine laboratory techniques. It is historically attributed to *Mycobacterium lepraemurium* (14,16). However, a number of new species have been identified using molecular methods, and nowadays is known that feline leprosy is actually caused by several species besides *M. lepraemurim,* such as *Candidatus* 'Micobacterium tarwinense', *Candidatus* "Micobacterium lepraefelis' and *Micobacterium visible* (17).

Feline leprosy is described worldwide and shows variable geographical prevalence among different species. *Candidatus* 'Micobacterium tarwinense' and *Candidatus* "Micobacterium lepraefelis' are, so far, exclusively reported in Australia and New Zealand, *M. visible* is documented in western Canada and some states of the USA, such as Idaho and Oregon, and *M. lepraemurium* has been described in several countries predominantly in temperate coastal areas (17) although it has been recently reported a case of *M. lepraemurium* infection in a cat living in an Alpine region in Switzerland, suggesting that the niche of *M. lepraemurium* may be wider than previously thought (18). The disease has not yet been reported in Latin America.

M. lepraemurium is the causative agent of murine leprosy and cats are accidentally infected. The transmission of the agent occurs thought fight wounds by rodent bites during hunting activities.

Therefore, adult male cats with outdoors access are at greater risk (5,7). Possibly, the transmission can also involve soil contamination of wounds, although an environmental niche where the pathogen can persist has not yet been recognized (16,19).

Panniculitis caused by non-tuberculous mycobacteria

Facultative pathogenic mycobacteria are saprophytes from soil, vegetation, water bodies and even tap water, and they can be responsible for opportunistic infections in humans and animals. These cases are most commonly related to rapid-growing species, but slow-growing variants can sometime be identified (5,7).

Rapid-growing mycobacteria isolated from cutaneous lesion in dogs and cats includes *M. smegmatis, M. goodii, M. fortuitum, M. chelonae, M.phlei, M. abscessus, M. flavescens, M. thermosistibile, M. margeritense, M. alvei* and *M. porcinum* (9,20). Less commonly, slow-growing mycobacteria such as *M. nebraskense, M. kansasii* and members of *Mycobacterium avium* complex can also result in infections (9,21,22).

These organisms are ubiquitous and distributed worldwide. There are geographical differences in causative species. The infection occurs after a penetrating injury and contamination of the wound by dirt and soil. Both cats and dogs can be affected, but cats are more prone to develop the disease probably because of their hunting and fighting behavior (5,7).

Rapid-growing mycobacteria, in humans and animals, are typically related to localized infections in immunocompetent hosts. The immunological response is usually effective in prevent disseminated disease. Immunosuppressed individuals by feline immunodeficiency virus (FIV) or feline leukemia virus (FeLV), use of immunosuppressive drugs, among others immunosuppressive factors, can develop disseminated disease (5,7). Infections caused by slow-growing variants can be associated with more disseminated disease, such as infections by members of *M. avium* complex that can cause systemic disease (5,7,9).

CLINICAL SIGNS

Canine leproid granuloma

Typically, CLG is presented as single or multiple dermal and subcutaneous nodular lesions predominantly located in dorsal fold of the pinna (10,11,12,15,23). The nodules are firm, well-circumscribed and may ulcerate, especially larger lesions. Pain and pruritus are not normally present, and lesions apparently do not bother the animal (10,11,12). The lesions can also occur on the head and may be rarely located in the trunk, rump and limbs, especially in bone prominences (10,11,23). Therefore, there is no significant spreading of lesion or systemic involvement, and affected dogs are otherwise healthy (10,11,12).

Feline Leprosy

Feline Leprosy is characterized by single or multiple granulomas in the skin and subcutaneous tissue, that can rapidly develop and became ulcerated (7,16). Lesions are usually painless and, although they can occur anywhere on the body, lesions tend to involve head, forelimbs, hindlimbs, body and tail/perineum (19). Peripheral lymphadenomegaly can be present (7,16).

Feline leprosy due to *Candidatus* 'Micobacterium tarwinense' can also involve ocular and periocular structures, including nictitating membrane, conjunctiva, and eyelids (17). Infections due to *Candidatus* "Micobacterium lepraefelis' are more propense to widespread and provoke potentially aggressive systemic disease (24).

Panniculitis caused by non-tuberculous mycobacteria

Infections with rapid-growing mycobacteria presents as granulomatous panniculitis, characterized by subcutaneous nodules that may ulcerate or fistulize. The lesion starts usually in inguinal and abdominal area after traumatic skin damage and subsequent wound environmental contamination and can spread through subcutaneous tissue to subjacent areas (5,7).

Infections by slow-growing mycobacteria, especially those from *M. avium* complex, are more commonly related to systemic disease with evolvement of multiples organs. Besides cutaneous lesions resembling those caused by other tuberculous or non-tuberculous Mycobacteria, cats, and dogs with disseminated disease may present weight loss, lethargy, lymphadenopathy, splenomegaly, pneumonia, gastrointestinal and neurological signs (7,9).

DIAGNOSIS

The various skin conditions caused by mycobacteria look similar and the causative species is clinically indistinguishable. Isolate and identify the species can be very challenging, because many species grow slowly in culture or even cannot be cultured at all. It is important to identify the causative agent involved whenever possible, especially because of the zoonotic potential of some species and to support therapeutical decisions.

Cytological examination should be attempted in all cutaneous lesions caused by mycobacteria. Obtaining samples by fine needle aspirations of nodular lesions usually provides the best specimens for this exam (5). Cytology reveals pyogranulomatous inflammation characterized by the presence of neutrophils, macrophages, and giant cells. The proportion of these different cells may vary according to causative species (25).

The thick cell wall rich in mycolic acid prevents standard Romanowsky-type stains to penetrate the microorganism. Therefore, under standard dyes, mycobacteria are seen as non-stained bacilli, intra or extracellular, forming negative or 'ghosts' images. Special stains for acid-fast bacilli, like Ziehl-Neelsen (ZN), reveal these organisms in a bright red color (25). Organisms number in cytological preparations can range from scarce to numerous among different mycobacteria infections (5,25).

Mycobacteria causes deep infections in the skin and histopathology typically reveals nodular to diffuse pyogranulomatous infiltrates, predominated by macrophages, in the dermis, the panniculus and the subcutis. The hematoxylin-eosin stain shows negatively stained organisms. For better visualization of the bacteria, ZN staining is preferable (26).

The number of organisms identified in histopathology is variable and depends on factors such as species involved, location of the lesion and host immune response (14). In canine leproid granuloma, bacillus load is highly variable (12,14). In feline leprosy, two histopathological forms are described, the lepromatous and the tuberculoid. The lepromatous form is characterized by a large number of mycobacteria and is associated with a poor cell mediated immune response. The tuberculoid form occurs with a robust cell mediated immune response and,

as a consequence, fewer organisms are identified (7,14,26). For its turn, the identification of the organisms in mycobacterial panniculitis can be very difficult, because the bacteria are often located in lipid vacuoles, and they can be lost during processing (5,7,14). Thus, a negative ZN stain does not rule out mycobacterial disease (27).

Mycobacterial culture is the reference standard diagnostic test for identification of the exact species present in the lesion. However, its sensitivity is low since some species are not easy to cultivate *in vitro* and others cannot be cultured at all. Still, a negative culture can be helpful, as it allows the exclusion of other relevant zoonotic mycobacteria, such as *M. avium* complex and *M. tuberculosis* complex. Therefore, material of suspected lesions should be always submitted to a reference laboratory for culture (1,5,14).

Molecular methods such as polymerase chain reaction (PCR) designed to amplify regions of the bacterial 16SrRNA gene are becoming increasingly available and allow to identify the causative species. Fresh tissue is the preferred sample to DNA extraction, but formalin-fixed, paraffin-embedded tissue can also be used for this technique, although fixation conditions may cause DNA degradation limiting the success of the procedure (5,14).

TREATMENT

Canine leproid granuloma

Lesions from CLG show benign behavior and may present spontaneous resolution within 1 to 3 months. For isolated lesions, surgical treatment may be curative, even without wide surgical margins. Additional therapeutic intervention can be required for persistent or severe lesions (5,14). In these cases, antibiotic therapy protocols include a combination of rifampicin (10-15mg/kg *per os*, once daily) and clarithromycin (7.5-12.5mg/kg *per os,* two to three times a day) or doxycycline (5mg/kg *per os,* twice daily) (5,28). There is also reported success with the use of enrofloxacin (5-10mg/kg *per os,* once or twice a day) and amoxicillin-clavulanic acid (22mg/kg *per os,* twice a day) in combination with topical rifamycin (29,30). Treatment must be continued until lesion resolution, and it takes up typically 4 to 8 weeks5.

Feline Leprosy

Spontaneous resolution of feline leprosy has already been described (31), but untreated lesions may spread to contiguous skin, lymph nodes and even internal organs. For these reasons, treatment should be started after diagnosis (14).

Surgical removal of small nodules, particularly those diagnosed early, might be curative (7) although lesions can relapse after surgery, especially when insufficient margins are obtained (14). Antimicrobial therapy should be started a few days prior to the surgery to ensure appropriate blood and tissue drug levels intra and postoperatively (5).

There are no guidelines for antimicrobials choice and duration of therapy (18). As the agents of feline leprosy cannot be cultured *in vitro,* susceptibility data are scarce. A combination of two or three antimicrobials effective against slow-growing mycobacteria are usually recommended (19), including clarithromycin (7.5-15mg/kg *per os,* twice a day), pradofloxacin (3mg/kg *per os*, once daily) and rifampicin (10-15mg/kg *per os*, once daily) and clofazimine (4-10mg/kg *per os,* once daily or 25-50mg/cat *per os,* once daily to once every 2 days) (14).

Panniculitis caused by non-tuberculous mycobacteria

Mycobacterial panniculitis in cats and dogs requires prolonged antimicrobial therapy, sometimes in combination with surgical resection (5). Depending on the size and location of the lesion, extensive surgical reconstruction may be necessary (32). Treatment should be continued 1-2 months beyond clinical resolution. Systemic disease requires 6-12 months of therapy (7).

Initially, oral antimicrobial can be chosen empirically, but once the susceptibility date is available, the optimal drug is selected. For slow-growing variants, susceptibility tests can take months to show results, so empirical therapy must be continued as long as required. Sensitivity patterns is often different among mycobacterial species (5).

Antimycobacterial agents such as rifampicin (10-15mg/kg *per os*, once daily), clarithromycin (7.5-15mg/kg *per os,* twice a day), doxycycline (5-10mg/kg *per os,* twice a day) and new-generation fluoroquinolones like marbofloxacin (2mg/kg *per os*, once daily), pradofloxacin (3-5mg/kg *per os*, once daily) and moxifloxacin (10mg/kg *per os*, once daily) are usually effective when used alone or in combination (7). It is recommended to use the highest possible dosage to ensure adequate drug concentrations in subcutaneous tissue (5). Mycobacteria can rapidly develop resistance against fluoroquinolones thus, it may be prudent not to use them as monotherapy (32).

ZOONOTIC CONCERNS

Zoonotic and interspecies transmission of non-tuberculous mycobacteriosis have never been described. However, the zoonotic potential of infected animals, regardless of the causative species, should not be underestimated. The risk of interactions between immunocompromised humans and infected companion animals has not been completely determined (9).

Moreover, infectious caused by zoonotic species from *M. tuberculosis* complex, such as *M. tuberculosis* and *M. bovis,* can result in cutaneous lesions clinically indistinguishable from those lesions caused by non-tuberculous mycobacteria. Thus, it is very important to identify the agent whenever possible and, until the organism is not known, considered it a potential zoonosis. Gloves should always be worn when handling those patients and prevent contact with exudations is strongly recommended (7).

CONCLUSIONS

The genus *Mycobacterium* comprises a wide-variety of species considered ubiquitous and adapted to different niches around the world. Some opportunistic species can cause dermal syndromes in dogs and cats diagnosed worldwide, although with variable geographical frequency. The environmental niche of these organisms is not fully known as well as their geographical distribution, thus it should be included in the differential diagnosis list for every patient with clinical aspects compatible with any of those syndromes. The diagnosis can be challenging and, considering the zoonotic potential of some mycobacteria and their different antimicrobial susceptibility, it is important to identify the causative agent involved whenever possible.

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