MYCOBACTERIAL INFECTIONS IN DOGS AND CATS
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Mycobacterial infections are rare in dogs and cats. In humans, the incidence appears to be on the rise as the consequence of a growing population of immunocompromised persons. The same may be true in pet animals as more undergo immunosuppressive therapy. Clinical disease with mycobacterial infections is variable, depending upon route of exposure, the infecting Mycobacterium species, and host factors. Multiple species of mycobacteria cause disease in dogs and cats and many of these species are zoonotic, which raises possible public health concerns. Caution may be advised when treating infected pets, particularly when the pets have contact with immunocompromised humans.

Fortunately, the risk for transmission of zoonotic species from pets to people is considered low.

During the last year (November 1, 2010 through October 31, 2011) nine cases of presumptive mycobacterial infections in cats and dogs were diagnosed from specimens received at Marshfield Labs (See Table 1). Five cases were in cats and four in dogs. Two cats with pyogranulomatous inflammatory disease suspicious for mycobacterial or nocardial disease were also diagnosed during this time period. Of these eleven cases, four of the diagnoses were made from cytology samples and seven from surgical biopsies.

GENERAL

The genus Mycobacterium is the only genus within the bacterial family Mycobacteriaceae of the order Actinomycetales. There are >70 identified species within the genus and new species are continuously being identified. Mycobacteria are gram-positive aerobic bacilli that cause disease in a variety of animal and bird species. All cause granulomatous or pyogranulomatous disease. Disease spectrum ranges from localized granulomas to disseminated disease with bacteremia. Localized disease tends to occur in immunocompetent hosts, while disseminated disease more frequently occurs in immunocompromised hosts. The location of a lesion can indicate the route of exposure. Most localized cutaneous granulomas result from direct contact through broken skin. Infections of the gastrointestinal tract or of intra-abdominal lymph nodes are most often caused by ingestion. Pneumonia usually is the result of breathing in contaminated aerosolized particles. It can be difficult to identify the site of entry when a patient presents with disseminated disease.

Strictly for clinical purposes, Mycobacterium species are sorted into different groups based upon their characteristic growth rates in culture. The ability to culture mycobacteria varies among the species. Species are characterized as being rapid-growers (<7 days to obtain a visible colony), slow-growers (>7 days to as long as weeks or months to obtain visible colonies) and difficult-to-grow (either very difficult or unable to cultivate in vitro). In-vitro growth rates tend to correspond to the severity of disease induced. In general, slow-growing mycobacteria cause more extensive disease

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and are the most difficult to treat. Rapidly-growing mycobacteria tend to cause more localized disease and are more likely treatable than slow-growers. However, these generalities are not fast rules since both slow-growing and rapidly-growing mycobacterial species can cause local or disseminated disease, even in immunocompetent hosts.

Canine and feline mycobacteria are categorized into three broad groups based upon their cultural growth patterns: 1) slow-growing: those of the Mycobacterium tuberculosis complex (M. bovis and M. tuberculosis) and of the slow-growing non-tuberculous mycobacteria (most commonly isolated of these are M. avium intracellulare-complex (MAC) species); 2) rapidly-growing: non-tuberculous mycobacteria; and 3) difficult-to-grow: mycobacteria that are the cause of leprosy syndromes in dogs and cats. The many species grouped into the rapid-growing non-tuberculous and slow-growing non-tuberculous mycobacteria are frequently referred to collectively as “atypical mycobacteria”, which can simply be translated to “mycobacteria that do not cause tuberculosis or leprosy”.

**SOURCES OF CANINE AND FELINE INFECTIONS**

**Slow-Growing Mycobacterium tuberculosis-complex**

Slow-growing mycobacteria of the M. tuberculosis complex are obligate pathogens. There are two species in this group that cause disease in dogs and cats of the United States: M. tuberculosis and M. bovis. Both are zoonotic. Both require reservoir mammalian hosts to survive. Mycobacterium bovis has a wide reservoir host range that includes cattle and wild animals, e.g., white tail deer in Minnesota and Michigan; badgers in Ireland; ferrets in New Zealand. Subclinical and clinical canine and feline infections with M. bovis occur. Although dogs and cats do not function as M. bovis reservoirs, they may transiently shed infective organisms into the environment. For this reason, infected dogs and cats are suspected to be potential sources of M. bovis infections for susceptible cattle and other animals, and for people. Mycobacterium tuberculosis has only one known reservoir - humans. Rare transmission of M. tuberculosis from an infected person to a dog or cat has been documented, presumably by prolonged contact with aerosolized or non-aerosolized bacteria-contaminated sputum or other material. There is also evidence of dog to dog transmission between co-housed animals during experimental infection. In contrast, there is only a single probable case of dog to human transmission that occurred during a necropsy of a dog with disseminated M. tuberculosis. There are no cases of M. tuberculosis transmission from cat to human. Because infected dog and cats are considered potential sources of human M. bovis or M. tuberculosis infection (albeit of very low risk), the recommendation is to not treat dogs and cats with these infections.

**Atypical Mycobacteria (Slow-Growing Non-tuberculous and Rapid-Growing Non-tuberculous)**

The “atypical” slow-growing non-tuberculous and rapidly-growing non-tuberculous mycobacteria are free-living saprophytes that are considered ubiquitous in nature and continuously encountered by animals and humans. Many are known to be zoonotic, but are not considered likely transmissible between animals and people. There is a single reported case of probable dog to human transmission of a rapidly-growing mycobacterium that occurred after prolonged direct contact with an infected skin lesion. The primary routes of exposure in dogs and cats to “atypical” mycobacteria are direct contact or ingestion of organisms from soil, water, or animal carcasses or feces; aerosolized transmission is considered less common. These organisms typically are isolated from water habitats (ponds, lakes, rivers, wet soils, tap water) and several of the species are more frequently isolated from tap water than from natural water sources. Interestingly, a variety of non-tuberculous mycobacteria have been isolated from the skin, upper respiratory tract, genital tract, and intestines of healthy people. Although these organisms are not considered normal resident flora of these sites, their relationship to human disease is not known. Organisms of the M. avium intracellulare-complex group of species can be present in feces, carcasses and raw meat from infected poultry or from other infected animal species, such as pigs, badgers, and white tailed deer. All species of non-tuberculous mycobacteria are considered of low virulence, typically causing severe disease only in immunosuppressed individuals.

**Difficult-to-Grow Leprosy Mycobacteria**

There is little known about the sources of the difficult-to-grow mycobacteria that cause the leprosy diseases of dogs and cats. There are no known human infections with any of the feline or canine leprosy mycobacteria and these organisms are not considered zoonotic. Mycobacterium lapraemurium of cats is believed to be transmitted by the bite of a rodent, but proof is lacking. The sources for feline M. visible and the several unnamed feline leprosy agents and for the mycobacterial agent of canine leprosy are not known. Insect bites are one hypothesized exposure route for canine leprosy.
A diagnosis of mycobacterial infection can be made from a cytology sample. A cytology diagnosis is based upon the staining characteristic of mycobacteria using routine Romanowsky cytology stains (Fig. 1A, Fig. 2, Fig. 3A). Mycobacteria do not stain with water-based Romanowsky stains typically used for cytology (includes Dif-Quik stain) due to the high lipid content of their cell walls. This is unique to the bacteria in the genus *Mycobacterium*. Mycobacteria are thus seen as non-staining (or “negative staining”) bacilli within macrophages or in smear backgrounds; the bacilli-shaped non-staining organisms are outlined by stained cytoplasmic or extracellular material. The identification of mycobacteria is frequently straightforward. If there is any question that non-staining bacilli-shaped structures are mycobacteria, an acid fast stain of the sample is performed to confirm the diagnosis. (Fig. 1B and Fig. 3B).

Diagnosing mycobacterial infections with a histology sample requires acid fast staining and may also require culture and/or PCR. As with Romanowsky cytology stains, mycobacteria do not typically stain with routine H&E, but in contrast to cytology, the non-staining bacteria are not visible in histopathology sections. A suspicion for mycobacterial infection is based upon the inflammatory cell population that is present in a lesion and this suspicion leads to acid-fast staining of the specimen. Unfortunately, bacteria of the genus *Mycobacterium* are not the only veterinary-relevant bacterial pathogens that stain positively with an acid fast stain; bacteria of genera *Nocardia* and *Rhodococcus* stain weakly positive. In rare cases in which nocardial or rhodococcal infections are still considered after acid fast staining, further testing involving culture and/or PCR might be needed to make a definitive diagnosis.

Even when a diagnosis of mycobacterial infection can be confirmed by cytology or histology, further diagnostics to identify mycobacterial group or species are recommended if treatment is considered. A tentative diagnosis of mycobacterial group can be made from lesion distribution and microscopic findings. However, this method is prone to error except for canine and feline leprosy syndromes, which have typical nodular cutaneous and subcutaneous lesions. There is considerable overlap in the clinical presentations of dogs and cats infected with mycobacteria of different groups, particularly between non-tuberculous slow-growers and non-tuberculous rapid-growers, making it highly possible for incorrect group designation based upon clinical disease alone. Incorrect group identification can result in inaccurate predictions of disease progression and of treatment response. Culture and/or PCR with gene sequencing are needed to make a definitive group +/- species identification. Culturing the organism and then performing PCR on a pure colony is optimal for species identification, but if a mycobacterial species belongs to either the difficult-to-grow group or slow-growing group, cultures can take weeks or the organism may fail to grow at all. In these cases, PCR performed directly on a submitted sample can be performed when the number of mycobacterial bacilli in the sample is large enough for PCR detection. PCR applied directly to submitted samples has succeeded ruling out *M. bovis* and *M. tuberculosis* infections, even when it failed to identify the infecting species.

**TREATMENT**

The potential for zoonotic transmission of mycobacteria from animal to human should be considered before initiating treatment. Although the risk for mycobacterial transmission from a dog or cat to a person is considered extremely low and even non-existent for some species, caution is advised when treating these diseases in animals, particularly if the patient has contact with immunocompromised people. Transmission risk is considered higher for immunocompromised people. Because there is evidence for transmission of *M. bovis* and *M. tuberculosis* between dogs and cats and humans, treating animal infections with either of these two species is not advised, regardless of owner immune status. People are more likely to be exposed to zoonotic species of slow-growing mycobacteria and rapidly-growing mycobacteria from the environment than from pets, but caution is recommended when treating infections in dogs and cats that have contact with immunocompromised persons. In this situation, treatment decision making should involve attending physicians. There is no public health concern with canine and feline infections with leprosy mycobacteria.

If treatment is considered, the prognosis for successful treatment needs to be assessed. Many canine and feline mycobacterial infections have a poor response to treatment. The prognosis depends upon a number of factors: the immunocompetence of the patient, the distribution of lesions, the infecting mycobacterial group or even individual species, and the susceptibility of the isolate to antimicrobials. For successful treatment, it is usually necessary to administer a combination of antimicrobials for a minimum of 3 months to more than 12 months.
with or without surgical debulking of localized lesions. It is highly recommended to ensure the patient is not immunodeficient, e.g., cancer chemotherapy and FeLV infection. Treatment of a known immunocompromised animal is not recommended due to poor treatment response. The distribution of lesions needs also to be determined. Immunocompetent animals have a good to guarded prognosis for treating localized disease, depending upon the locations of the lesions and the particular infecting mycobacterial species. Unfortunately, the prognosis for treating disseminated disease even in immunocompetent animals is typically poor, although success has been achieved.

For optimal treatment of mycobacterial infections, antimicrobial susceptibility testing of a cultured isolate is performed when possible. But, it is also advised to immediately start treating before culture or PCR results are available. Single drug use is discouraged because this increases the opportunity for the isolate to develop antimicrobial resistance. There are established treatment protocols for the different groups of mycobacteria that have been derived from previous treatment data. Susceptibility testing is recommended because it can determine if chosen drugs are likely to be effective or if the isolate is already resistant to any of the drugs; and it can also reduce the chance of promoting resistance. If an organism cannot be cultured, sometimes PCR and DNA sequencing applied directly to a submitted sample can be helpful; there are reported drug susceptibilities for mycobacteria with specific DNA sequences. Work is ongoing to develop methods of faster culturing of slow-growing mycobacteria and to improve molecular diagnostics on samples taken directly from lesions.

**Atypical Mycobacteria**

- **Slow-Growing Non-Tuberculous**
  
  Slow-growing non-tuberculous mycobacteria are the most difficult to treat. Even though these organisms take over a week to culture, culture with susceptibility testing is advised for optimizing antimicrobial selection. Some of these species tend to produce numerous organisms within lesions and PCR performed directly on submitted samples may be possible even if susceptibility testing cannot be performed. Genetic sequencing data can help when choosing antimicrobials. Localized lesions of slow-growing non-tuberculous mycobacteria, such as those of the *M. avium intracellulare* complex (MAC), can be cured, but prognosis is always guarded. Cats with MAC frequently present with localized lymph node and/or cutaneous lesions, which may be treatable. There are also several reported cases of successfully treated disseminated MAC disease in Abyssinian cats. Dogs typically present with disseminated MAC that responds poorly to treatment. Other non-tuberculous slow-growing mycobacteria have been isolated from lesions in dogs and cats, both from localized and disseminated disease; unfortunately, these organisms are thought to mainly cause disease in immunosuppressed hosts and the prognoses are always considered guarded to poor.

- **Rapid-Growing Non-Tuberculous**

  The rapidly-growing non-tuberculous mycobacteria overall carry a better chance for successful treatment than slow-growing non-tuberculous mycobacteria. Susceptibility testing of cultured isolates is strongly recommended. There are many identified species within this group and dogs and cats have been infected with a number of them. Clinical presentation varies from local granulomatous panniculitis to pneumonia to disseminated disease. For both dogs and cats, the prognosis for treating localized infections of any of the rapid-growing non-tuberculous species is considered guarded to fair. Localized disease in immunocompetent hosts is the most common presentation and surgical debulking, when possible, accompanied by antimicrobials can achieve complete resolution of disease. Disseminated disease even in immunocompetent patients carries a poor prognosis.

**Difficult-to-Grow (Leprosy)**

Mycobacteria of this group cannot be cultured by routine methods. Direct PCR on samples might be achievable, but the lesions caused by these organisms have a typical cutaneous nodular pattern and diagnosis is often made from lesion distribution in conjunction with cytology or histology. Treatment protocols are not well established. Leprosy diseases of cats behave somewhat differently than the leprosy disease of dogs. Leprosy in cats is caused by more than one species and prognosis is dependent on species and disease distribution. *Mycobacteria lapaemurum* characteristically is seen in young immunocompetent cats and prognosis depends on the extent of lesions when diagnosed. This feline leprosy syndrome tends to be aggressive and difficult to cure if discovered when locally extensive, but if discovered when very localized, excision combined with medical treatment can be curative. Two other leproid mycobacterial diseases of cats are not yet speciated and clinical syndromes and
treatment responses not established. One leprosy agent of cats, putative *M. visibile*, has been isolated in cats from Canada and northwestern United States and presents with widespread cutaneous to disseminated disease; successful treatment has been reported even when lesions are disseminated. Canine leprosy, caused by a single as yet unnamed mycobacterial agent, has an excellent prognosis for a complete cure. Canine leprosy is a localized cutaneous/subcutaneous infection, typically on the head or ears, that is treated by excision combined with antimicrobial therapy; lesions may even spontaneously resolve.

**SUMMARY**

Mycobacteria cause granulomatous or pyogranulomatous disease. Clinical presentation depends upon the route of exposure, the *Mycobacterium* species, and host factors. A diagnosis of mycobacterial infection can be made with cytology alone or with acid fast staining of histology samples. Species identification requires DNA sequencing of a cultured sample or may possibly be achieved with PCR applied directly to a submitted sample. Most mycobacterial infections in dogs and cats have minimal public health concerns; however, concern increases when infected pets have contact with immunocompromised people. All mycobacterial diseases carry poor prognoses in immunocompromised hosts and good to poor prognoses in immunocompetent hosts, depending on *Mycobacterium* species and disease distribution. Treatment of mycobacterial diseases is long-term, often many months.

Table 1

Mycobacterial cases in dogs and cats diagnosed from submissions to Marshfield Labs, November 1, 2010 through October 31, 2011.

<table>
<thead>
<tr>
<th>Signalment</th>
<th>History</th>
<th>Sample</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>CATS</td>
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<tr>
<td>5-month-old, FS, DSH</td>
<td>Mass in cervical area non-responsive to antibiotics, 2-month duration</td>
<td>Histology: cervical lymph node</td>
<td>Pyogranulomatous cellulitis and lymphadenitis with scattered extracellular acid fast bacilli of <em>Mycobacterium</em> or <em>Nocardia</em></td>
</tr>
<tr>
<td>4-year-old, MN, DSH</td>
<td>Submandibular and popliteal lymphadenopathy, several-week duration</td>
<td>Histology: submandibular and popliteal lymph nodes</td>
<td>Severe diffuse pyogranulomatous submandibular and popliteal lymphadenitis with intracellular acid fast bacilli</td>
</tr>
<tr>
<td>5-year-old, FS, DSH</td>
<td>Subcutaneous mass of left inguinal region</td>
<td>Histology: subcutaneous mass excision</td>
<td>Pyogranulomatous panniculitis and lymphadenitis; few small aggregates of extracellular acid fast bacilli</td>
</tr>
<tr>
<td>10-year-old, MN, DSH</td>
<td>Soft neoplasm on bridge of nose, 1-month duration</td>
<td>Histology: fragments of surgically excised nasal mass</td>
<td>Pyogranulomatous/lymphoplasmacytic inflammation with moderate numbers of intracellular acid fast bacilli of <em>Mycobacterium</em> or <em>Nocardia</em></td>
</tr>
<tr>
<td>12-year-old, MN, DSH</td>
<td>Small intestinal mass and other intra-abdominal masses; weight loss; PD/PU; diarrhea</td>
<td>Histology: surgical biopsy of small intestine mass</td>
<td>Neutrophilic, histiocytic lymphoplasmacytic and eosinophilic inflammation with many intracellular acid fast bacilli</td>
</tr>
<tr>
<td>12-year-old, FS, breed unknown</td>
<td>Consolidation of lungs; subcutaneous swelling on dorsum/left chest area; mild fever; wheezing</td>
<td>Cytology: aspirates of 1) subcutaneous swelling and 2) lungs</td>
<td>1) Neutrophilic and histiocytic inflammation with many intracellular and extracellular non-staining bacterial bacilli 2) Mixed cellular inflammation with rare intracellular non-staining bacilli</td>
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<table>
<thead>
<tr>
<th>17-year-old, FS, DSH</th>
<th>Alopecic bump on ventral chin, ~2-week duration</th>
<th>Cytology: bump on ventral chin</th>
<th>Granulomatous inflammation with many intracellular and extracellular non-staining bacilli</th>
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</thead>
<tbody>
<tr>
<td><strong>DOGS</strong></td>
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<tr>
<td>1-year-old, FS, Shi Tzu</td>
<td>Submandibular, prescapular, and popliteal lymphadenopathy</td>
<td>Cytology: aspirates of left and right prescapular and right submandibular lymph nodes</td>
<td>Benign lymphoid hyperplasia to pyogranulomatous lymphadenitis with presence of many non-staining intracellular and extracellular bacilli</td>
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<td></td>
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<td></td>
<td>Left prescapular lymph node culture + 16S PCR and DNA sequencing: <em>M. avium intracellulare</em>-complex – susceptible to clarithromycin + (ethanbutol and rifampin combination)</td>
</tr>
<tr>
<td>3-year-old, MN, Boston Terrier</td>
<td>Intradermal mass</td>
<td>Histology: surgical biopsy of intradermal mass</td>
<td>Pyogranulomatous deep dermatitis and panniculitis with low numbers of extracellular acid fast bacilli</td>
</tr>
<tr>
<td>4-year-old, FS, Boxer</td>
<td>Alopecic lesion on dorsal edge of pinna, non-responsive to oral antibiotics or dermatophyte topical treatment</td>
<td>Histology: skin punch biopsies of pinna lesion</td>
<td>Severe pyogranulomatous and lymphoplasmacytic dermatitis with scattered intracellular acid fast bacilli</td>
</tr>
<tr>
<td>9-year-old, FS, Husky</td>
<td>Mild lymphadenopathy and thickened intestines; ultrasonographically mottled spleen</td>
<td>Cytology: Aspirate of spleen</td>
<td>Granulomatous inflammation with intracellular non-staining bacilli</td>
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</table>

Figure 1. Fine needle aspirate of peripheral lymph nodes of a dog.

A: Dif-Quik stain. Granulomatous lymphadenitis with negative-staining intracellular *Mycobacterium* bacilli.  
B: Acid fast stain. Pink-staining *Mycobacterium* bacilli in macrophages.

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Figure 2. Fine needle aspirate of cutaneous lesion on a cat. Dif-Quik stain. Pyogranulomatous inflammation with negative-staining intracellular Mycobacterium bacilli.

Figure 3. Fine needle aspiration of mesenteric lymph node in a ferret.


Bibliography


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