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Mycobacterial disease in a population of 339 cats in Great Britain: II. Histopathology of 225 cases, and treatment and outcome of 184 cases

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This study investigated 339 cases of feline mycobacterial infection, with histopathology findings from 225 cases, and treatment and outcome information from 184 cases. Tissue samples from cats with cutaneous lesions or suspicious masses at exploratory laparotomy were submitted to the Veterinary Laboratories Agency for mycobacterial culture over a 4-year period to December 2008. The study reviewed the files for information about histopathology, treatment and outcome, and blindly reviewed histopathological changes (including staining for acid-fast bacteria [AFB]) in a sub-set of 45 cases. When a cat is suspected of having a mycobacterial infection, accurate identification of the species involved helps to determine possible treatment options and prognosis. The study confirmed that histopathology and the presence of AFB are useful tools in the recognition of mycobacterial infection. Unfortunately, they did little to help determine the species of mycobacteria involved. The study identified a group of cats that were negative for AFB at the primary laboratory, but from which mycobacteria could be cultured; commonly *Mycobacterium bovis* or *Mycobacterium microti*. The study also identified a group of cats which where culture negative, despite typical signs of mycobacterial infection and positive AFB staining. Many cases responded favourably to treatment (56% of the cases where information was available), and many cats gained complete remission (42%). However, relapses were common (64%) and often followed by pulmonary and/or systemic spread that may have resulted from treatment with short courses of single drugs. This study shows that the diagnosis and treatment of feline mycobacteriosis is complex and challenging.

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Mycobacterial infections in humans and other animals are of international concern.[1–3] One mammalian species that can be infected by a number of different mycobacteria is the domestic cat. Unfortunately, many aspects of feline mycobacteriosis remain unknown, and there have been few recently published research papers on this subject.[4]

Diagnosis of feline mycobacterial disease can be challenging. It is usually made by finding suggestive histopathological changes in biopsies and identifying morphologically typical acid-fast bacteria (AFB),[5–8] with confirmation by specialist culture of fresh tissue.[9] However, many samples fail to culture and those that do can take up to 3 months to grow.[10] Specific tests such as serology and intradermal testing have generally proved unhelpful in cats,[7,9,11,12] although the interferon (IFN) gamma test and other immunoassays are showing promise in detecting and differentiating cats infected with *Mycobacterium bovis*, *Mycobacterium microti* and *Mycobacterium avium*.[13–15] Molecular [polymerase chain reaction (PCR) and sequencing-based] tests have been developed and are now being used more commonly; however, they are expensive and have low sensitivity when only a few mycobacterial organisms are present.[8,16–20]

Treatment of mycobacterial infection in cats is complicated, and successful outcomes are more likely

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when the species of mycobacteria has been identified and the cat has been treated with a long course of multiple appropriate drugs, plus surgery (where indicated).[4,9,21–26] To date, there are no drugs approved for the treatment of mycobacterial infections in animals and the 'recommended' treatment regimes for cats (under the United Kingdom's Cascade procedure) are based on clinical experience, rather than controlled clinical trials. In addition, deciding to treat a cat with mycobacteriosis can be contentious, particularly if *M bovis*, *M microti* or *M avium* are involved, as these infections are potentially zoonotic, particularly to humans with compromised immune systems.[9,27] Treatment of a cat with an *M bovis* infection is particularly contentious, as under the Tuberculosis Orders in force in England, Wales, and Scotland the suspicion or identification of *M bovis* infection in a cat is notifiable (DEFRA 2008[28]). Unfortunately, tubercle group bacteria and non-tubercle group mycobacteria (NTM) can cause similar clinical signs,[4,10] and because successful culture may take many weeks,[10] many cats commence treatment in the interim, sometimes being given inappropriate drugs, risking the development of antibiotic resistant mycobacterial clones.[29]

Given the paucity of our knowledge about feline mycobacterial disease in Great Britain (GB) the primary aim was to carry out a field survey to assess the histopathological changes caused by these infections; determine how these infections are currently treated; and assess their current prognosis. By knowing which bacteria are present, it is possible to determine which cases are appropriate to treat, which are more likely to respond to treatment and how best to tailor the treatment protocols. It is particularly important to identify cats infected with *M bovis*, *M microti* and *M avium* as these have significant potential zoonotic risk. As culture can take up to 3 months[10] and access to molecular diagnostics is limited, the secondary aim of the study was to determine if the histopathological findings could enable prediction of which mycobacterial species is present.

Materials and methods

Tissue samples

Between January 2005 and December 2008, 339 feline samples were submitted to the veterinary Laboratory Agency (VLA) Weybridge by veterinary surgeons in GB for mycobacterial culture.[30] Culture was performed free of charge following the introduction of Tuberculosis Orders in England, Wales, and Scotland, and was funded by DEFRA. The samples came from cats that had been found to have cutaneous lesions or suspicious masses at exploratory laparotomy, and when formalin-fixed samples were sent to private pathology laboratories for histopathology the tissue was found to have lesions suggestive of mycobacterial infection (typical granulomatous and/or pyogranulomatous inflammation consisting of multifocal to coalescent infiltration with large numbers of macrophages containing variable numbers of AFB).[6] The veterinary surgeons then took a second sample and submitted it without fixation to the VLA for mycobacterial culture. Depending on the availability of material, either swabs, impression smears or fixed material was stained with Ziehl Nielsen (ZN) for the detection of AFB.[31] Histopathology findings were available from 225 cats from the primary diagnostic laboratory and 93 from the VLA.

Veterinary surgeons that submitted the samples to the VLA were contacted by one of the authors (SMcF) and asked to provide information on histopathological changes found within the lesions, the course of disease progression (development of respiratory and/or systemic signs, radiographic or ultrasound changes), treatment details (surgery, drugs given, duration of treatment), and eventual outcome (remission, relapse, euthanasia or death). Data on where the cat lived (ie, the postcode of the owner's house), plus the cat's signalment (age, breed, gender), and clinical presentation are presented in the accompanying paper.[32] In many cases the information was incomplete or not available so where data were missing the number of samples included in the analysis has been noted.

To investigate the variation in histopathology between cats infected with different *Mycobacterium* species, samples from tissues of 45 animals were selected for detailed retrospective examination. This was not a random selection of cases as care was taken to include as many possible culture outcomes as possible (please see the sister paper for detailed information about which species of mycobacteria were cultured from the 339 cats and how commonly each species was identified).[32] However, within each group of samples infected with a particular *Mycobacterium* species, samples were retrieved at random from the tissue archive. This selection process resulted in 15 *M bovis* samples (28% of *M bovis* samples in the study), 13 *M microti* (21%), five *M avium* (21%), one *Mycobacterium malmoense* and 11 samples with lesions where culture was negative (6%). The samples were examined without knowing the culture result by a single experienced histopathologist (author AS). Lesions were assessed for the presence of epithelioid cells, neutrophils, extent of necrosis, presence of multinucleated cells and semi-quantitatively for the number of AFB. The numbers of AFB were assessed using the following criteria: '0.5' − AFB difficult to find, '1' − one AFB every three to four high powered field (HPF), '2' − AFB easy to find and '3' − cells contain very large numbers of AFB. Necrosis was scored as '0' − none present, '1' − some necrosis, '1A' − autolytic and therefore difficult to judge, '2' − moderately extensive necrosis, and '3' − multifocal to coalescent necrosis. If multiple samples were present for a single animal, the mean score was calculated for final evaluation.

Statistical analyses

Two groups of factors were considered for analyses: (i) diagnostics and (ii) treatment. For each group