Case Report

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Successful treatment of vaginal malakoplakia in a young cat

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Abstract

Case summary A 3-year-old, female, spayed, domestic shorthair cat presented for dysuria and haematuria, unresponsive to antibiotic treatment. A small, fleshy, erythematous mass protruded from the vaginal vault. Ultrasound identified a vaginal mass effect with mixed echogenicity measuring in excess of 3 cm. Vaginoscopy confirmed an extensive, fleshy, irregular mass that was characterised histologically as pyogranulomatous vaginitis, with periodic acid–Schiff-positive macrophages containing gram-negative bacteria. Fluorescence in situ hybridisation analysis demonstrated invasive intracellular *Escherichia coli*. Vaginal malakoplakia was diagnosed. Tissue culture and antimicrobial susceptibility of *E coli* was used to guide treatment. A 6 week course of enrofloxacin 5 mg/kg q24h resulted in complete resolution of the mass and clinical signs.

Relevance and novel information Malakoplakia is a rare chronic inflammatory condition that has been previously reported in the bladder of two cats. The pathogenesis of malakoplakia is thought to involve ineffective killing of bacteria (eg. *E coli*), similar to granulomatous colitis in Boxers and French Bulldogs. The literature on malakoplakia in cats is sparse. This is the first reported feline case with vaginal involvement, intracellular *E coli* and successful treatment with a fluoroquinolone. Malakoplakia is an important, non-neoplastic differential diagnosis when a mass is identified in the urogenital system of a young cat.

Introduction

Malakoplakia is a rare, chronic inflammatory condition that has been described in humans for over 100 years, most commonly involving the urinary bladder of middle-aged women, although other parts of the urinary tract and, rarely, other organs can be involved.[1] Only more recently has this condition has been described as a spontaneous disease in animals, including two kittens, three pigs, and a cynomolgus monkey.[2–7] The term was originally created to describe soft, plaque-like lesions seen within the urinary bladder that were thought to be neoplastic.[1] Grossly, human malakoplakia lesions vary from flat plaques to nodules and masses that resemble tumours.[1] Histology reveals the inflammatory nature of the lesions, which are characterised by large numbers of histiocytes (referred to as von Hansemann cells) containing periodic acid–Schiff (PAS)-positive cytoplasmic granules. Basophilic intrahistiocytic inclusions known as Michaelis–Gutmann bodies are regarded as pathognomonic, and are described in many cases.[1,8]

The pathogenesis of this disease is unclear, but it is often linked to a bacterial infection such as *Escherichia coli*, with 80–90% of people diagnosed with malakoplakia having a persistent coliform urinary tract infection.[9] Immunosuppression or an innate host immune defect also could play a role, with some cases of malakoplakia reported in humans with AIDS, neoplasia or receiving immunosuppressive therapy for another disease.[1,8,10]

Descriptions of malakoplakia frequently identify bacteria associated with histiocytes on light or electron microscopy, and the Michaelis–Gutmann bodies may represent mineralised accumulations of phagolysosomes.[1,11] It has been speculated that this disease is a consequence of impaired bacterial killing by macrophages, perhaps associated with ineffective assembly of microtubules.[1,11] Experimental studies support this theory; with similar lesions created in the kidney and testes of rats by injection of *E coli* lipopolysaccharide

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extracts, and in the skin of pigs by subcutaneous injection of *Rhodococcus equi*.[11–13] The microscopic appearance of these lesions, and the identification of *E coli* within them has been compared with *E coli*-associated granulomatous colitis in Boxers and French Bulldogs.[4,14,15] A recent study of affected Boxers and French Bulldogs revealed genetic polymorphisms in a region of chromosome 38, which includes loci encoding signalling lymphocytic activation molecule family glycoproteins; these have been linked to impaired killing of *E coli*,[16,17] consistent with the proposed pathogenesis of malakoplakia.

This report describes a case of malakoplakia involving the vagina of a young cat; a novel location for the disease in animals, the first report describing intracellular *E coli* associated with feline malakoplakia, the second report of successful treatment of this disease, and also the first report of successful treatment with enrofloxacin.

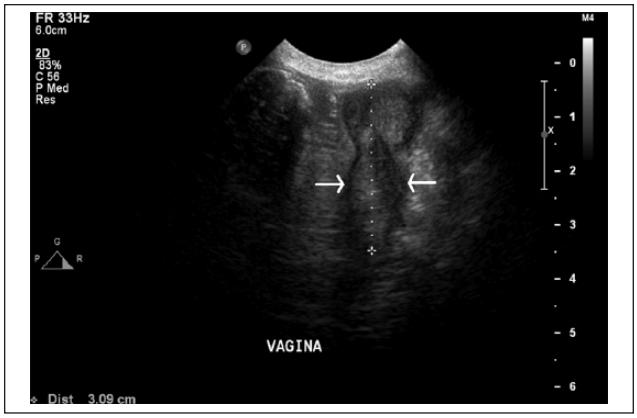

Figure 1 Longitudinal view of the vaginal mass, with calipers demonstrating the craniocaudal extent of the lesion. White arrows indicate the location of the lesion

Case description

A 3-year-old, female, spayed, domestic shorthair cat was presented to the primary veterinary clinic for malaise, anorexia, stranguria, periuria, pollakiuria and macroscopic haematuria. The cat had no previous pertinent medical history, and had been spayed at 5 months of age, with no abnormalities or complications noted during or after surgery.

No abnormalities were noted on clinical examination, and the cat was prescribed an empirical 6 day course of amoxicillin/clavulanic acid tablets at 12.5mg/kg q12h (Clavulox; Zoetis Animal Health).

This treatment did not result in improvement, prompting a revisit 1 week later. A cystocentesis sample revealed well-concentrated urine (specific gravity 1.050), with microscopic haematuria and trace protein noted on dipstick evaluation. No urine culture was performed. A soft, proliferative mass was seen protruding from the vulva; a grab biopsy sample of this tissue was collected under general anaesthesia. Pending histopathology the cat was prescribed prednisone orally at 5 mg q12h for 7 days, reducing it to 5 mg q24h for 7 further days and further amoxicillin/clavulanic acid at the previous dose. Dietary management included a specific veterinary diet (Urinary Care; Royal Canin).

Histopathology at a reference laboratory (New Zealand Veterinary Pathology, Hamilton) revealed dysplastic squamous epithelium, with moderate numbers of neutrophils, macrophages and activated fibroblasts, resulting in a diagnosis of chronic granulomatous and proliferative vaginitis with marked epithelial dysplasia.

Despite initial improvement with the new treatment regime, malaise, lethargy, vaginal swelling, macroscopic haematuria and periuria persisted, and so the cat was referred to an internal medicine specialist for further evaluation.

On presentation to the Veterinary Specialist Group, the sole abnormality noted on physical examination was a small, fleshy, erythematous mass protruding from the vaginal vault.

Feline immunodeficiency virus and feline leukaemia virus ELISAs were negative (SNAP FIV/FeLV combo; IDEXX Laboratories).

Abdominal ultrasound (iE35, C8-5 probe; Philips) identified free-floating and slowly settling echogenic debris and a single, 2.7 mm diameter mineralised structure revealing gravity dependence within the urinary bladder. The urinary bladder wall thickness was within expected normal limits.

Imaging from a perineal window identified a vaginal mass effect greater than 3 cm in size with mixed echogenicity, a hyperechoic centre and a hypoechoic periphery (Figure 1). The caudal limits of the lesion had a bulbous shape while the cranial limits revealed a thickened fusiform shape. The bulbous shape was approximately 1.3 cm in diameter.

Vaginoscopy, performed under general anaesthesia using a 3.5 mm rigid endoscope (64019 BA, 1030340 camera, DX PAL 202420-20 processor; Karl Storz) identified an extensive, fleshy, friable, irregularly shaped mass with diffuse attachment to the mucosa within the vaginal vault. Thick, firm, white exudate was present, particularly around the cranial aspect of this lesion. It was difficult to discern normal anatomy owing to the pathology present. Extensive debridement and biopsy of abnormal tissue was performed with 2.8 mm round-cup biopsy forceps (FB-35C-1; Olympus). The urethral orifice was not visible; however, a urinary catheter was passed blindly to ensure urination after mass debridement.

Culture of the fresh tissue at a reference laboratory (Gribbles Veterinary, Auckland) produced a heavy growth of *E coli*, sensitive to amoxicillin/clavulanic acid,

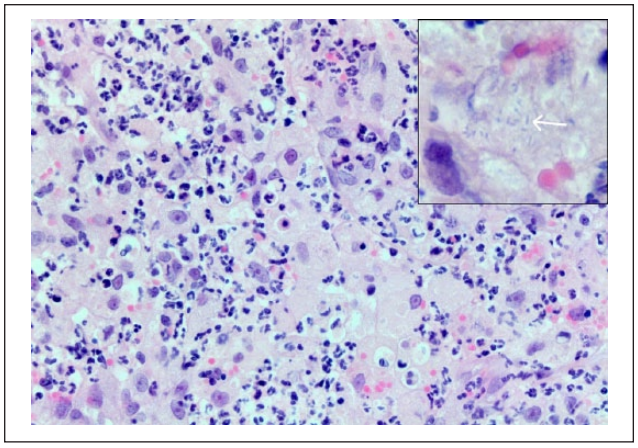

Figure 2 Pyogranulomatous inflammation composed predominantly of neutrophils and macrophages. Faint basophilic objects consistent with bacterial rods are visible in macrophages (see inset, indicated by white arrow). Haematoxylin and eosin, × 50

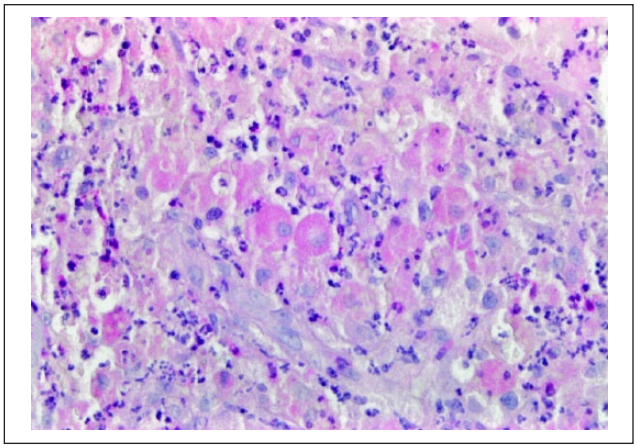

Figure 3 Macrophages contain variably prominent periodic acid–Schiff-positive granules (PAS, × 50)

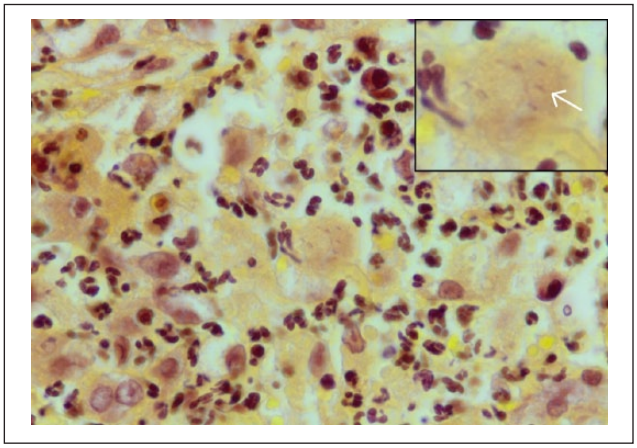

Figure 4 Macrophages contain gram-negative bacterial rods (see inset, indicated by white arrow). Gram stain, × 100

cephalothin, enrofloxacin, trimethoprim sulpha, polymyxin B and neomycin by standard disc diffusion testing.

The cat was hospitalised with the urinary catheter in situ for 48 h, and then discharged with no complications noted. In the light of the culture, sensitivity and histopathology results, enrofloxacin (Baytril; Bayer Animal Health) was prescribed at a dose of 5 mg/kg q24h for 6 weeks. This resulted in rapid and complete resolution of the clinical signs and the cat is clinically normal 1 year after treatment.

The biopsy samples were fixed in 10% neutral buffered formalin before routine histological processing and embedding in paraffin wax. On histopathological examination the biopsies were well preserved, and lined by dysplastic squamous epithelial cells; similar cells also formed cords, islands or glandular/ductular structures infiltrated by neutrophils within the samples (presumed dysplastic vestibular glands). The adjacent stroma was heavily and diffusely infiltrated by neutrophils, lymphocytes and plasma cells admixed with many macrophages (Figure 2). These had abundant, faintly granular eosinophilic cytoplasm, with variably strong PAS-positive staining (Figure 3). The macrophages sometimes contained a neutrophil, vacuolated space or short bacterial rods, found to be gram-negative on Gram staining (Figure 4); similar rods were also seen apparently within neutrophils. These were not acid-fast with Ziehl–Neelsen stain. No basophilic bodies were seen within macrophages on haematoxylin and eosin or von Kossa stains.

Unstained sections (5 µm on charged glass slides) of formalin-fixed, paraffin-embedded tissue were submitted to Cornell University for fluorescence in situ hybridisation (FISH) analysis with a eubacterial probe and an *E coli* probe as described previously.[14] Specificity of hybridisation was controlled by co-hybridisation with an irrelevant labelled probe (non-EUB-338 [ACTCCTACGGGAGGCAGC-6-FAM]), and the use of control slides of cultured *E coli*, *Streptococcus* species and *Proteus* species. Hybridised samples were washed in phosphate-buffered saline, allowed to air dry and mounted with a ProLong antifade kit (Molecular Probes). Sections were examined on an Axioskop 2 (Carl Zeiss) or a BX51 (Olympus America) epifluorescence microscope, and images were captured with a Zeiss Axiocam or Olympus DP-7 camera, respectively. Multifocal clusters of short- and medium-sized rods that hybridised with eubacterial probe 338 were visualised within cells that were consistent with macrophages within mucosa. These bacteria also hybridised with *E coli/Shigella* species probe, indicating the presence of intramucosal infection with *E coli* (Figure 5).

Discussion

This is the first reported feline case of malakoplakia with vaginal involvement, intracellular *E coli* and successful treatment with a fluoroquinolone.[2,4] Reports to date suggest that malakoplakia is an important differential

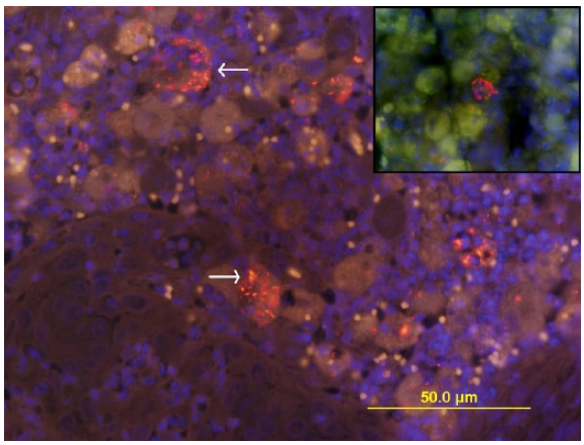

Figure 5 Fluorescence in situ hybridisation (FISH) analysis of vaginal mucosa. Eubacterial FISH revealed multifocal clusters of intracellular rods within the vaginal mucosa (arrows). These bacteria hybridised with an *Escherichia coli/Shigella* species probe (inset). Bacteria (Cy3) are red/orange. Nuclei (4′,6-diamidino-2-phenylindole) are blue

diagnosis for lower urinary tract disease in a young cat, especially when a granulomatous mass is identified involving the urogenital system and, especially as these reports illustrate that this condition is treatable, in contrast to comments from another source.[18]

This case had PAS-positive macrophages and invasive gram-negative bacteria but did not have the Michaelis–Gutmann bodies that are considered pathognomonic for malakoplakia in people.[1] However, their absence does not preclude a diagnosis of malakoplakia as they are not uniformly present or easily detected in malakoplakia in people or animals.[1,5,19] Smith described three stages of malakoplakia lesion development in humans, with the first (early) stage characterised by plasma cells, macrophages, eosinophils and an absence of Michaelis–Gutmann bodies.[19] An experimental study involving the injection of *E coli* into the kidneys and testes of rats produced lesions resembling those described in Smith's stages, with Michaelis–Gutmann bodies appearing later in the disease process.[13] Garrett and McClure had similar findings but suggested an alternative explanation that the dose of *E coli* stimulus dictated whether or not Michaelis–Gutmann bodies formed.[12] In this case, the lesion location (close to the urethral orifice), microscopic appearance, presence of *E coli* and response to therapy lead to the diagnosis of pyogranulomatous vaginitis/vestibulitis consistent with malakoplakia.

Abnormalities were noted within the urinary bladder with ultrasound. However, further investigation and treatment was directed at the obvious mass present in the vagina, with a plan to address the urinary bladder if the clinical signs did not resolve. It is unclear whether these changes were related to malakoplakia.

The microscopic appearance of these lesions, and the identification of *E coli* within them has been compared to Whipple's disease of humans,[1] and granulomatous colitis of Boxers and French Bulldogs.[14,15] It is relevant to this case that PAS-positive macrophages are found in granulomatous colitis, but invasive bacteria are rarely seen on routine histopathology, and Michaelis–Gutmann bodies have not been reported in those lesions.[4]

Intracellular bacteria were not identified in the two case studies in cats, although *E coli* was cultured from the bladder wall and urine of one kitten.[2,4] FISH was performed in this case, in addition to Gram staining and histopathology, to confirm the presence of intracellular bacteria. Culture of tissue enabled the selection of strain-specific antibiotics.

Successful treatment with long courses of antibiotics capable of penetrating macrophages is common in human malakoplakia,[10] and has recently been reported in one of the kittens with urinary bladder lesions.[4] The second reported feline case, also in the urinary bladder, was diagnosed post mortem.[2] It is interesting to note that the cat described herein was initially unsuccessfully treated with antibiotics to which the organism was susceptible *in vitro*. This is similar to a previous cat, which eventually responded to sulfamethoxazole and trimethoprim, in conjunction with amoxicillin and clavulanic acid.[4] Antibiotics other than fluoroquinolones, or trimethoprim/sulfamethoxazole, have not been effective in human medicine.[10] It has been hypothesised that penetration of antibiotics into macrophages may be important in treatment success in people,[10] and fluoroquinolone antibiotics are known to achieve this.[10,20,21] One review of the human literature suggested long courses of fluoroquinolone antibiotics have a cure rate of 90%.[10] The importance of combining antimicrobial sensitivity with the ability to penetrate macrophages is pivotal for successful treatment of *E coli*-associated granulomatous colitis in Boxers.[22]

Consistent with the two previous cats in the literature, this cat was young.[2,4] This is in contrast to humans, where the average age of presentation is >50 years, and 40% of people have concurrent systemic illness.[8] We are aware of another case of malakoplakia recently diagnosed in Christchurch, New Zealand, in the urinary bladder of a 3-month-old kitten (R Fairley, 2016, personal communication), suggesting that malakoplakia is more common in young cats than previously thought. A survey of pathologists showed a low rate of correct identification of the classic histological appearance of this disease in people,[9] which may also be the case in domestic animals, resulting in misdiagnosis.

Conclusions

This report provides further evidence that malakoplakia is a treatable disease that needs to be considered as a differential diagnosis for lesions within the urogenital

tract of cats, especially if young. This case report describes a unique presentation, and the first case of malakoplakia outside of the urinary bladder in a cat, and the first responding to enrofloxacin. Further study would be beneficial to clarify the pathogenesis and prevalence of this disease, along with optimal treatment strategies.

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