Pyogranulomatous skin disease and cellulitis in a cat caused by *Rhodococcus equi*

This report describes a case of *Rhodococcus equi* infection causing pyogranulomatous skin disease and cellulitis in a two-year-old female domestic shorthaired cat. The case differed from previously reported cases in cats in its clinical presentation and in the locations of the lesions, which were similar to those seen in horses. The presence of an intracellular organism was confirmed by cytology and on histopathology. The aetiological diagnosis was confirmed by routine biochemical tests specific for *R equi* on a pure isolate obtained from a biopsy specimen. The report also reviews the literature of the documented feline cases and discusses the common pitfalls in the diagnosis of such infections.

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INTRODUCTION

Rhodococcus equi (previously known as *Corynebacterium equi*) is an intracellular pathogen that establishes itself in macrophages by interfering with phagolysosomal fusion (Heitala and Ardans 1987). This interference eventually results in the multiplication of the pathogen within the macrophages, which leads to the formation of granulomas and, eventually, necrosis. The aerobic Gram-positive pleomorphic organisms of *R equi* vary from cocci to rods and are commonly found in the faeces of foals and in soil contaminated by other herbivore faeces. The organism has also been isolated from rabbit and bird droppings, but not from cat faeces (Carman and Hodges 1987).

R equi mainly causes pyogranulomatous bronchopneumonia in foals, with gastrointestinal involvement in about 50 per cent of the cases (Giguere and Prescott 1997). It has also been reported to cause ulcerative lymphangitis, cellulitis, subcutaneous abscesses and arthritis in horses (Zink and others 1986, Perdrizet and Scott 1987). It is known to cause infections in humans with defective cell-mediated immune responses and those on immunosuppressive treatment. About 30 per cent of infected human patients have a history of having been in contact with contaminated herbivore faeces (Prescott 1991). There have also been sporadic reports in the literature of *Rhodococcus* infections in cats associated with mediastinal and mesenteric lymphadenitis (Jang and others 1975) and cellulitis and abscesses, mainly of the extremities (Higgins and Paradis 1980, Elliot and others 1986, Oxenford and others 1987, Fairley and Fairley 1999).

The present report describes a clinical presentation in a cat involving the neck and submandibular lymph node, which resembles ulcerative lymphangitis, cellulitis and pyogranulomatous disease, as seen in horses. It also describes the cytological, microbiological and histopathological findings and discusses the common pitfalls in the diagnosis of this unusual cause of pyogranulomatous disease in the species.

CASE HISTORY

A two-year-old neutered female domestic shorthaired cat was presented with a large ulcerated mass on the left side of the neck. According to the owner, a lump had occurred on the right side of the neck following a cat fight. Swab specimens, submitted by the referring veterinary surgeon, had identified the presence of *Staphylococcus intermedius* and β-haemolytic streptococci on three previous occasions. On the first two occasions, histopathological examination of biopsy specimens revealed a pyogranulomatous dermatitis and cellulitis. On the third occasion, intracellular organisms were found within macrophages. The organisms did not stain acid-fast with Ziehl-Neelsen (ZN) stain, but they did stain positive with periodic acid Schiff (PAS) stain.

Despite excisions with wide surgical margins and antibacterial therapy with 5 mg/kg enrofloxacin (Baytril; Bayer Animal Health) followed by 5·5 mg/kg clindamycin (Antirobe; Pharmacia and Upjohn Animal Health) twice daily, new lesions continued to appear. The cat's condition slowly deteriorated, with the onset of pyrexia, anorexia and lethargy as the

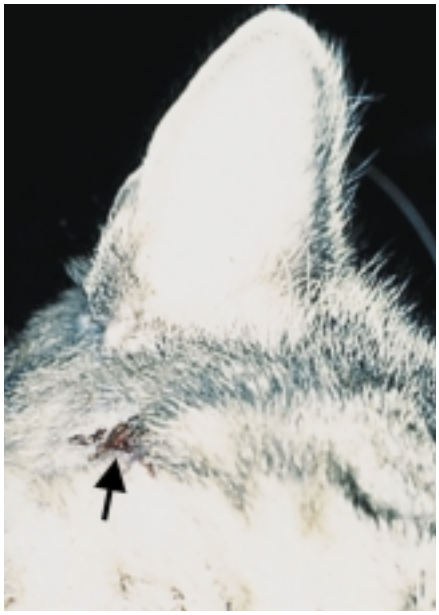

FIG 1. Haemopurulent exudate from a draining tract (arrow) over the right parotid gland

Table 1. Infectious agents responsible for granulomatous skin disease in cats

		Aetiological agents
Bacteria	Non-acid-fast organisms	*Actinobacillus* sp, *Arcanobacterium pyogenes* (previously known as *Actinomyces pyogenes*), *Rhodococcus equi*, *Staphylococcus* sp, *Streptococcus* sp, *Pseudomonas* sp, *Proteus* sp
	Acid-fast organisms	*Norcardia asteroides, Mycobacterium lepraemurium, M tuberculosis, M microti, M chelonei, M fortuitum, M phlei, M thermoresistible, M smegmatis*
Fungi	Subcutaneous mycoses	*Microsporum canis, Rhizomucor* sp, *Mortierella* sp, *Fusarium* sp, *Paecilomyces* sp, *Alternaria* sp, *Cladophialiophora* sp, *Exophiala* sp, *Moniliella* sp, *Curvularia* sp, *Madurella* sp, *Pythium insidiosum, Sporothrix schenckii*
	Systemic mycoses	*Cryptococcus neoformans, Sporothrix schenckii, Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis*
Protozoa		*Leishmania* sp

disease progressed, at which point the cat was referred.

On referral, a general physical examination revealed the cat to be in poor condition, weighing 2·9 kg, with a temperature of 39·4°C. On auscultation, the cat was found to be tachycardic, with a heart rate of 170 beats per minute. No abnormal lung sounds were detected.

The submandibular and the right prescapular lymph nodes were enlarged. However, the left prescapular lymph node was not palpable because the lesion was at the site of the node. There was a haemopurulent discharge from a draining sinus over the right parotid gland (Fig 1) and a large non-painful ulcerated mass of about 4 cm diameter, with seropurulent exudate, on the left prescapular area (Fig 2). The surface of the mass had a crater-like appearance, with exposure of the underlying subcutaneous fat and muscle. The surrounding skin was alopecic, but surface lesions were not visible. On palpation, the mass was not circumscribed and crepitus was felt under the skin, suggesting deeper involvement.

Differential diagnoses at this stage included granulomatous dermatitis caused by infectious bacterial, fungal or protozoal organisms (see Table 1).

Haematological analysis demonstrated a leucocytosis ($19{\cdot}2 \times 10^9$/litre; reference range 5 to 18 $\times 10^9$/litre) with a mature neutrophilia ($15{\cdot}1 \times 10^9$/litre; reference range 4 to 14 $\times 10^9$/litre). Serum biochemical analysis revealed a raised creatine kinase concentration (132 iu/litre; reference range <120 iu/litre). All other parameters were within the normal reference ranges. An ELISA and virus isolation for feline leukaemia virus antigen and immunofluorescence for feline immunodefiency virus antibodies were negative. The antibody titre for feline coronavirus was 1/10.

Impression smears taken from the surface of the ulcerated mass and the draining tract from the right lymph node were stained with modified Wright's stain (Diff-Quik; Dade AG) and examined under an oil immersion lens. Numerous neutrophils and macrophages containing cocci and rod-shaped organisms within clear vacuoles

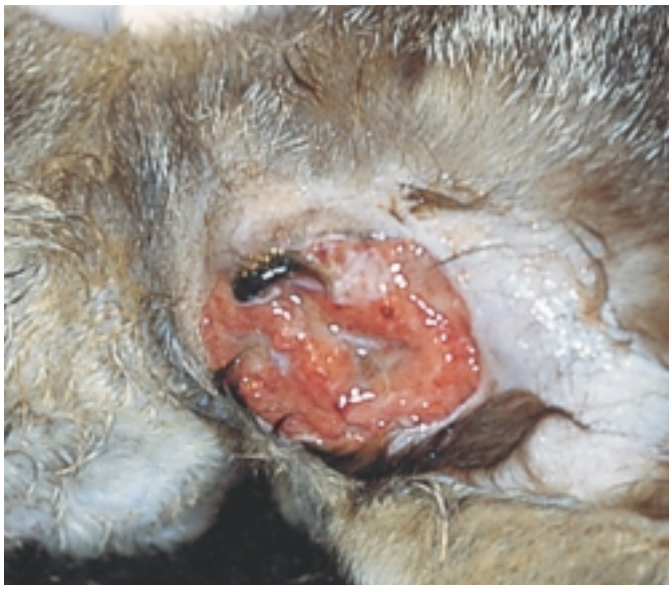

FIG 2. Appearance of the ulcerated mass on the left lateral neck

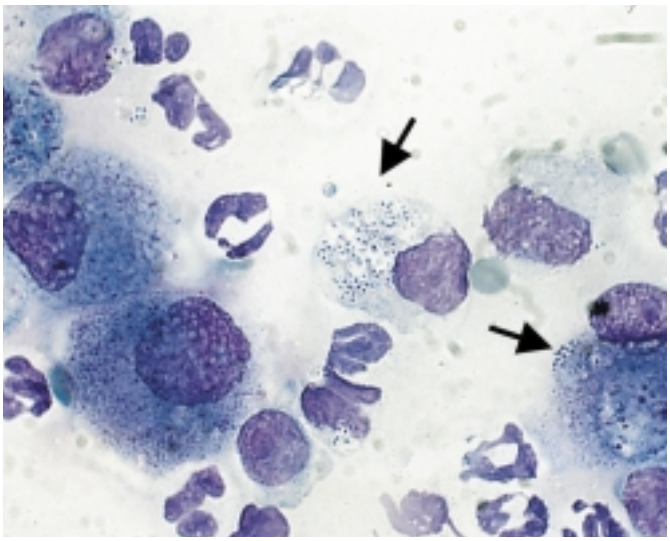

FIG 3. Intracellular organisms within the macrophages (arrows) and segmented neutrophils found on an impression smear stained with modified Wright's stain. ×1250

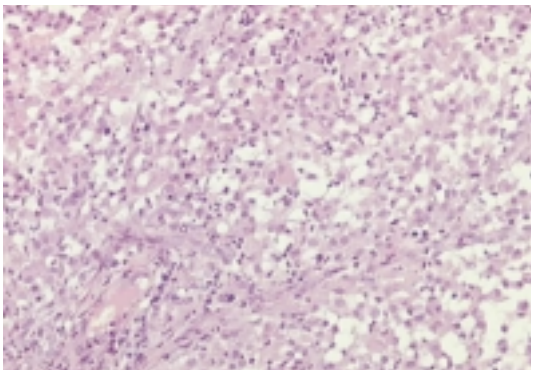

FIG 4. Diffuse pyogranulomatous reaction. Haematoxylin & eosin ×125

in the cytoplasm were seen (Fig 3).

Several biopsy specimens were obtained under anaesthesia induced with 80 mg/kg medetomidine (Domitor; Pfizer Animal Health), 0·4 mg/kg butorphanol (Torbugesic; Fort Dodge Animal Health) and 5·0 mg/kg ketamine (Ketaset; Fort Dodge Animal Health), injected intramuscularly from one syringe. Biopsy specimens from the centre of the ulcerated mass and from the surrounding skin were submitted for histopathological examination and a sample from each site was submitted for bacterial, mycobacterial and mycological culture. Thoracic and abdominal radiographs did not reveal any abnormalities.

R equi was recovered from the tissue biopsy submitted for bacteriological analysis. The organism showed in vitro susceptibility to enrofloxacin, cefuroxime and oxytetracycline. It was resistant to penicillin, ampicillin, coamoxiclav, cephalexin and co-trimoxazole. Microscopic examination and culture from biopsies were negative for acid-fast bacteria (Mycobacterial Reference Laboratory, Cardiff) and for fungi (Mycological Reference Laboratory, Bristol).

Histopathological examination of the tissue from the ulcerated lesion revealed a diffuse pyogranulomatous reaction (Fig 4) containing foamy macrophages, within which small coccoid organisms were present. Within the same biopsy there was evidence of infiltration of mononuclear cells into the muscle tissue. Biopsies from the surrounding area showed diffuse dermatitis, with focal aggregates of lymphoid follicles and deep pyogranulomatous panniculitis. The macrophages within the panniculus also contained numerous intracellular organisms.

A diagnosis of cellulitis and subcutaneous abscess caused by *R equi* was made. A guarded prognosis was given, because of the extent and the chronic nature of the condition. Doxycycline (Ronaxan; Merial Animal Health), at 10 mg/kg every 12 hours, was administered. Despite supportive therapy and antibiotic treatment the cat died within two weeks of diagnosis. A postmortem examination of the thoracic and abdominal organs did not reveal any gross abnormalities. Because of the time lapse between death and necropsy, further samples were not submitted for culture.

DISCUSSION

At the time of writing, 11 cases of *R equi* infections in cats have been reported and all but three of these involve either the digits or other extremities (Higgins and Paradis 1980, Elliot and others 1986, Fairley and Fairley 1999). In the remaining three cats, internal abcessation and lymphadenitis were diagnosed (Jang and others 1975, Oxenford and others 1987). In two of these three cats, the findings were made at postmortem examination, whereas in the remaining one, infection was postulated to have caused pneumonia (Fairley and Fairley 1999).

The present report describes a case where cellulitis, abscessation and ulcerative lymphangitis were present in the same cat. In view of the zoonotic potential of some of the organisms causing granulomatous disease in cats, it is important that the cause of the disease in such cases is precisely identified.

Details of the sampling techniques used to detect *R equi* have not been reported before. In the present case, routine culture techniques using swab samples failed to identify the organism. Using this technique, several morphologically distinct colonies appeared on the plates and the technician inspecting the plate selected those suspected to be pathogens for identification. In this case, *Staphylococcus intermedius* and β-haemolytic streptococci were isolated from swab specimens taken on different occasions. It is possible that on these occasions the laboratory may have misidentified the colonies of *R equi* as contaminants or that they may not have grown at all from a swab specimen, since it is an intracellular pathogen. Similar difficulties also appear to have been encountered in human microbiology laboratories (Doig and others 1991).

The biopsy specimens were submitted to specialist laboratories for fungal, mycobacterial and bacterial cultures. The laboratory involved in the bacterial culture was alerted to the possibility that aerobic and anaerobic bacteria, such as *R equi*, *Norcardia asteroides*, *Arcanobacterium* species and *Actinobacillus* species, could be present. The technique of culturing organisms from a tissue specimen involves crushing the material to release the intracellular organisms. In this case, the technique produced a pure culture of *R equi*, which was then easy to identify using routine biochemical tests for the species.

This report emphasises the need to submit biopsy specimens for culture when trying to identify intracellular pathogens and also the importance of alerting the laboratory to what possible organisms they need to look out for.

PAS, a tissue stain mainly used to identify fungal elements in biopsy specimens, produces a red colour when positive. It sometimes also stains glycogen, neutral mucopolysaccharides and tissue debris (Scott and others 2001). The presence of mucopolysaccharides within the bacterial cell wall may account for the positive staining seen in the present case, which could have been misleading. However, fungal spores and bacteria can be differentiated from each other by their size on microscopic examination.

Of the 11 reported cases of *R equi* infection in cats, four either died or were euthanased. Seven survived, so the prognosis seems to be reasonably favourable when

there is no systemic infection present. In the most recent report, five out of six cats with lesions involving distal extremities recovered after antibacterial treatment, whereas one with a suspected infection of the lungs died (Fairley and Fairley 1999).

Elliott and others (1986) suggested that it might be possible to transfer the organism from one animal to another via a fomite. Therefore, the various attempts to remove infected tissue by wide margin excision by the referring veterinary surgeon may have failed due to the spread of infection during surgery, or because it may already have spread via the lymphatic system. It is postulated that in the present case the organism probably spread via the latter route, because following the initial infection on the right side of the neck, the right submandibular lymph node and parotid gland became involved, and because the clinical signs bore close resemblance to those of ulcerative lymphangitis seen in horses, pigs and ruminants.

A variety of antibacterial agents have been used in the treatment of *R equi* infection. The isolate in this report was sensitive to enrofloxacin, cefuroxime and oxytetracycline. Based on these results, doxycyline was prescribed. A previous attempt at treatment with enrofloxacin had shown a poor response. Tetracyclines act by inhibiting protein synthesis through binding to the 30-S ribosomal subunit, which prevents the transfer RNA from binding to its receptor site on the ribosome (Papich 1995). Doxycyline is lipid-soluble, which gives it the ability to achieve good intracellular penetration, and it has been advocated as a second-line treatment for other intracellular pathogens, such as opportunistic mycobacterial infections (Gunn-Moore and Shaw 1997). The cat in the present report may not have responded to doxycycline because of the extensive spread of the organism, even though in vitro sensitivity had been demonstrated.

Naturally occurring infections most commonly occur in foals through inhalation of the infectious agent (Giguere and Prescott 1997). In humans, *R equi* infections have mostly been reported in association with immunosuppressive diseases or therapy. It has been most commonly reported in those which have developed AIDS, those suffering from malignancies and those undergoing chemotherapy and organ transplant treatment (Prescott 1991).

Using mouse models it has been demonstrated experimentally that immunosuppression caused by cyclophosphamide and corticosteroids can result in similar infections to those seen in naturally occurring equine cases (Bowles and others 1989). In vitro studies have shown that *R equi* is able to multiply and persist within macrophages (Hondalus and Mosser 1994). In vivo studies in mice have demonstrated that this ability is correlated with the presence of a virulence-associated plasmid, which allows bacterial multiplication within the macrophage and granuloma formation (Hondalus 1997). This virulence-associated plasmid has been found consistently in *R equi* isolates from clinically affected foals, but not from clinically affected humans, suggesting that the patient's immunodeficiency status allows the less virulent strains to persist within the macrophages.

Conclusions

An underlying cause for infection was not identified in the present case, nor in any of the previously reported feline cases. However, bearing in mind that this is an opportunistic organism and with increased use of immunosuppressive treatments in both cancer therapy and, more recently, in organ transplantation in feline medicine, both clinicians and laboratory technicians should not overlook the potential pathogenicity of this organism. Early identification and appropriate treatment may allow successful treatment.

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