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SYSTEMIC INFECTION DUE TO *CANDIDA PARAPSILOSIS* IN A DOMESTIC FERRET (*MUSTELA PUTORIUS FURO*)

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Abstract

An 18-month-old castrated male ferret (*Mustela putorius furo*) was presented to the veterinary hospital for acute collapse but died despite initiation of emergency treatment. The body was submitted for a complete postmortem examination. The pathologist determined the ferret was suffering from severe necrotizing encephalitis, necrogranulomatous mediastinal lymphadenitis, and ulcerative dermatitis attributable to systemic *Candida parapsilosis*. This is the first report of systemic *Candida parapsilosis* in a ferret. Copyright 2014 Elsevier Inc. All rights reserved.

Key words: *Candida parapsilosis*; encephalitis; ferret; *Mustela putorius furo*; systemic infection

Systemic fungal diseases are uncommon in the domestic ferret (*Mustela putorius furo*), with single documented cases of blastomycosis,[1] candidiasis,[2] coccidioidomycosis,[3] histoplasmosis,[4] and mucormycosis[5] in ferrets. In recent years, multiple cases of cryptococcosis[6-10] have also been described in ferrets. However, only a single case of candidiasis due to *Candida albicans* has been described in this species.[2] Although considered less virulent than *C. albicans* and *Candida tropicalis*, *Candida parapsilosis* is challenging the former as a cause of fungemia in hospitals across the world. Candidemia is the fourth most common cause of hospital-acquired bloodstream infection in the United States and the developed world, accounting for more than half of all episodes of sepsis in nonneutropenic patients in an intensive care unit or surgical ward.[11] A surveillance study of bloodstream infections in the United States, Canada, Latin America, and Europe from 1997 to 1999[12] reported that more than 55% of bloodstream infections were due to *C. albicans*, 15% were due to *Candida glabrata* and *C. parapsilosis*, and 9% were due to C. *tropicalis*. The proportion of non–C. *albicans* species causing candidemia differed according to geographic location, with 45% in the United States and 55% in Latin America. *C. glabrata* accounted for 21% of the non–*C. albicans* species in the United States, and *C. parapsilosis* accounted for 25% in Latin America, 16% in Canada, and 17% in Europe. Similar trends were reported by 2 of the authors 6 years later,[13] and in a recent study of data from Australia, Belgium, Brazil, and Greece.[14] *C. parapsilosis* has a greater incidence of bloodstream infections in children than in adults,[13] and this organism is a known pathogen of the young.[15] This is the first report of a systemic fatal infection in a domestic ferret caused by *C. parapsilosis*, characterized by the formation of a space-occupying lesion within the mediastinum and severe encephalitis.

CASE HISTORY

An 18-month-old, castrated male, domestic pet ferret was evaluated for severe lethargy that rapidly progressed to acute collapse. The ferret was fed commercially available pellets (Supreme Science Selective Ferret, Supreme Petfood Limited, Suffolk,

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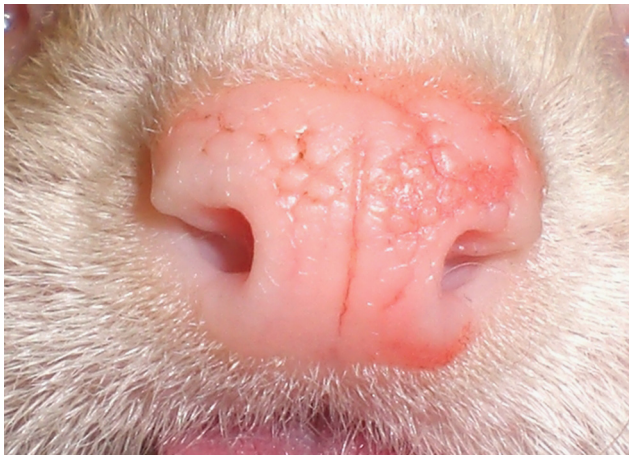

FIGURE 1. Gross appearance of a ferret with systemic *Candida parapsilosis*. The nose appeared ulcerated and hyperemic. On histological examination, ulceration and perivascular dermatitis were evident.

UK) offered ad libitum and occasionally supplemented with raw eggs and meat. The animal was kept in an outdoor wire enclosure with 7 other ferrets but frequently brought indoors. The ferret had free access to water and there was no history of trauma, toxin exposure, or any other previous health problems. All the other household members (i.e., animals and humans) had no overt clinical disease and remained healthy during and after their cagemate disease and death. The ferret patient was up to date on its vaccination status for canine distemper virus (CDV). The morning the ferret was presented to the veterinary hospital, it had not emerged to feed and was very lethargic. On presentation at the clinic, the patient was laterally recumbent, poorly responsive, and appeared in moderate body condition (body weight 1.2 kg; body condition score 2.5/5). Physical examination revealed pale mucous membranes, a capillary refill time >2 seconds, a body temperature of 36.4°C (97.5°F) and mild dehydration. Other physical examination findings were unremarkable. Immediate emergency treatment was instituted. A 26 g intravenous catheter was placed into the right cephalic vein. Warmed lactated Ringer solution was administered at 10 mL/kg/h via a syringe pump (Graseby MS16A, Smiths Medical MD, Inc, St. Paul, MN USA). The ferret was placed on a water recirculating heat pad (TPump professional, Gaymar, Orchard Park, NY USA) to gradually increase his body temperature. A Doppler probe (Ultratec PD1v, Thames Medical, West Sussex, UK) was applied to the left carpus and held in place by adhesive tape. Indirect blood pressure measurement was taken and was found to be constantly less than 40 mm Hg. A slow bolus of 5 mL/kg intravenous hetastarch (Voluven 6%; Fresenius Kabi Ltd, Cheshire, UK) was provided. Despite the emergency treatment, the ferret's clinical condition deteriorated rapidly over a 15-minute period until he was completely unresponsive. Respiratory and cardiac arrest occurred and cardiopulmonary and cerebral resuscitation were performed. The ferret was intubated with a 2-mm uncuffed endotracheal tube that was connected to an Ayre T piece and he was manually ventilated. Cardiac compressions were immediately started through the chest wall. Doxapram (Dopram-V injection, 20 mg/mL, Fort Dodge Animal Health Ltd, Hampshire, UK) and adrenaline (Epinephrine injection 1:1000, Martindale Pharmaceuticals, Essex, UK) were administered intravenously at 5 mg/kg and 0.5 mg/kg, respectively. Fluid therapy was continued and 2 intravenous boluses of 3 mL/kg of hetastarch were repeated 10 minutes apart. Resuscitation was unsuccessful and the ferret died. No antemortem diagnostic testing was performed on the ferret.

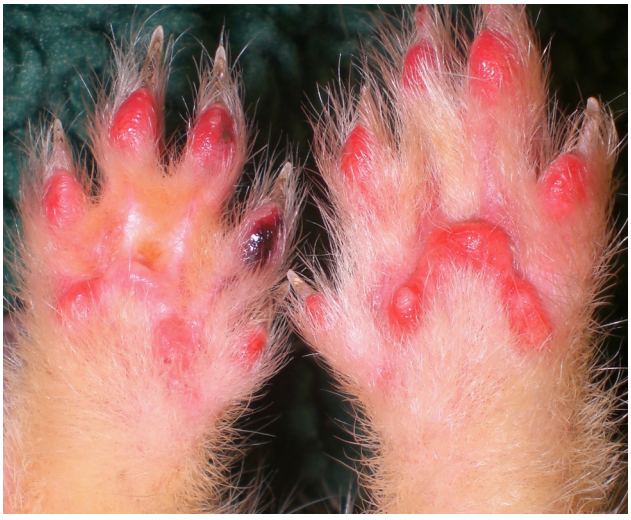

FIGURE 2. Gross appearance of a ferret with systemic *Candida parapsilosis*. The footpads of all 4 feet presented with full-thickness epidermal necrosis and ulceration. Histological examination revealed ulceration and perivascular dermatitis.

The ferret was submitted for complete postmortem examination. Immediately after death, the carcass was stored in a refrigerator. It was then packaged in accordance with current legislation and sent by next day delivery to the pathology laboratory (IZVG Pathology, Yeadon, Leeds, UK). The postmortem examination was performed on the day following the ferret's death by a qualified anatomical pathologist. On external assessment, the nares were ulcerated and hyperemic (Fig. 1). Other mucous membranes (e.g., conjunctiva, anus, and oral cavity) were pale

pink but smooth and intact. Full-thickness epidermal necrosis and ulceration affected the footpads of all 4 feet (Fig. 2). The bronchial lymph node at the bifurcation appeared moderately enlarged and a further 25-mm-diameter ovoid, multinodular mass was present on the right side of the mediastinum, distinct and immediately cranial to the cranial lung lobe. The outer surfaces of the multilobular mass were irregular with cream, raised foci and a translucent gray capsule. Cut surfaces were firm, smooth, and oozing a red-gray mucopurulent material. The external surface of the brain was unremarkable, but after fixation, slicing revealed cavitating foci of malacia and hemorrhage involving the inner cerebral cortex and thalamic nuclei (Fig. 3). No additional macroscopic abnormalities were recognized in the remainder of the carcass. A range of tissue samples were collected from the body and fixed in 10% buffered formalin for routine histological examination. A sample of the mediastinal mass was also submitted for bacterial and fungal culture studies.

Multiple histological sections of the mediastinal mass had remnants of lymph node largely effaced by multifocal to coalescent necrosis, hemorrhage, and fibrogranulomatous inflammation that contained numerous bulbous, branching, aseptate fungal pseudohyphae (Fig. 4). Fungal invasion and granulomatous vasculitis were present in large arteries. Extensive invasion by similar fungi was present within the bronchial lymph node. Much of the forebrain, including the thalamus and cerebral cortex, was disrupted by multifocal liquefactive necrosis, hemorrhage, and inflammation, again with abundant invading fungal pseudohyphae lacking obvious septation (Fig. 5). Bacterial cultures yielded no aerobic or anaerobic growth, but selective fungal cultures produced a heavy growth of a *Candida*-like organism. This was subsequently identified by the Leeds Regional Mycology Reference Laboratory, based on morphological and cultural characteristics, as *C. parapsilosis*. Histological examination of a full range of organs identified mild centrilobular vacuolar change in the liver that may have been consistent with hypoxia or anemia but could also have been a terminal change. Extramedullary hematopoietic tissue was abundant in the spleen, but this is a common idiopathic finding in adult ferrets. There was no evidence of dysplasia or neoplasia in hematopoietic populations or of disseminated leukemic infiltrates in any organ examined.

Multiple skin sections from nasal planum and footpads displayed full-thickness epidermal ulceration and superficial perivascular dermatitis.

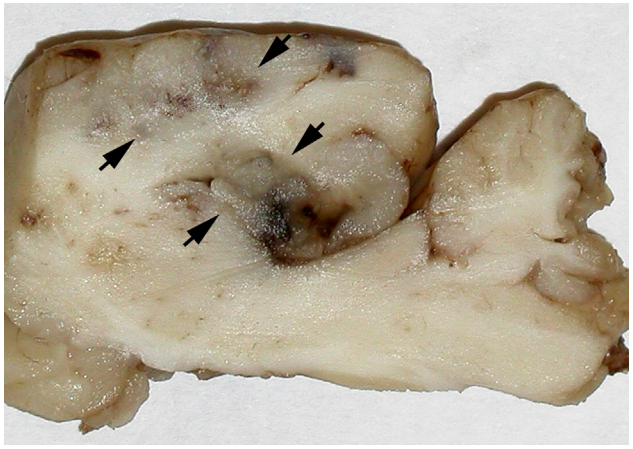

FIGURE 3. Formalin-fixed cut surface of the brain after fixation. The tissue slices revealed cavitating foci of malacia and multifocal areas of hemorrhage involving the cerebral cortex and thalamic nuclei (indicated between arrowheads). Histological examination revealed liquefactive necrosis associated with hemorrhage.

Eroded surfaces were colonized by mixed populations of bacteria and small numbers of broad-based budding "cottage-loaf" periodic acid–Schiff stain–positive yeast (*Malassezia* sp.) (Fig. 6). No pseudohyphae were identified to correspond with those in the mediastinum or brain.

Real-time polymerase chain reaction (PCR) and reverse transcriptase real-time PCR were performed for CDV and Aleutian disease virus (ADV) on frozen (−80°C, -112°F) spleen samples submitted (Scanelis, Toulouse, France) after thawing and fixation in absolute ethanol. Results were positive

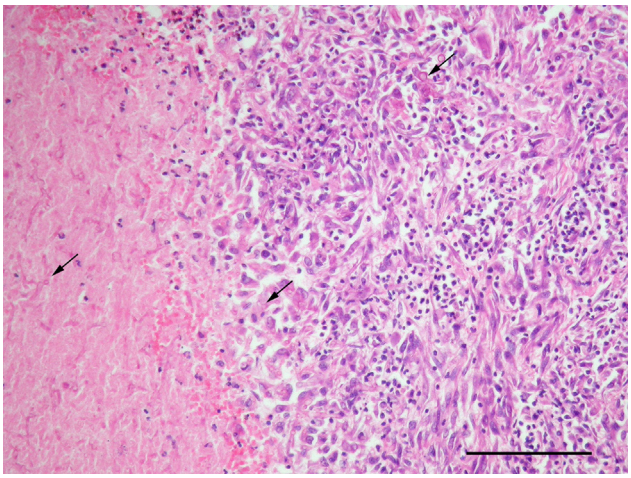

FIGURE 4. Histological section of the mediastinal mass, including remnants of lymph node, central necrosis, and surrounding suppurative to fibrogranulomatous inflammation containing bulbous, branching, aseptate fungal pseudohyphae (examples highlighted by arrows). Hematoxylin and eosin, scale bar 100 μm.

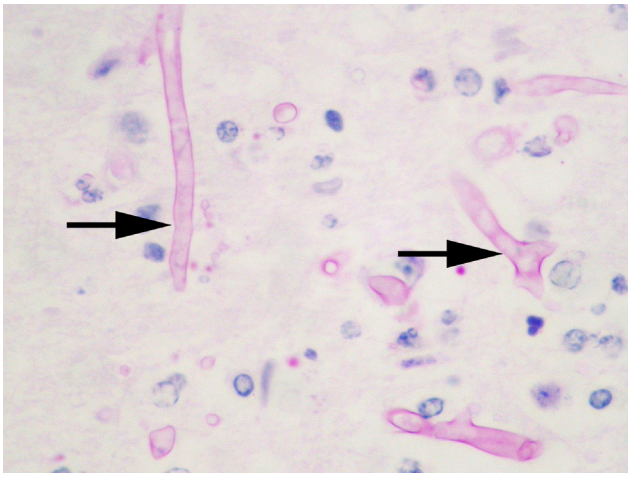

FIGURE 5. Histological section of the forebrain with abundant fungal pseudohyphae lacking obvious septation (arrows). Periodic acid–Schiff, magnification ×1200.

for CDV (very low load). Typing suggested a vaccine strain. The sample was negative for ADV.

DISCUSSION

To the authors' knowledge, this is the first report of systemic candidiasis in a ferret caused by *C. parapsilosis* with development of a space-occupying cranial pyogranulomatous mediastinal mass and necrotizing encephalitis. The initial gross impressions were inconsistent with a toxic etiology and suggested against an infectious disease process.

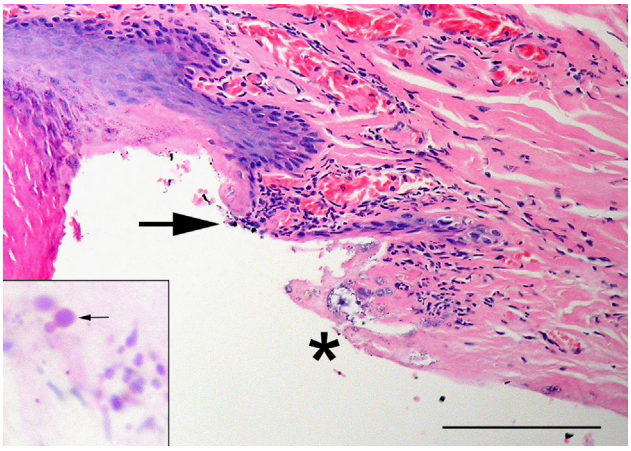

FIGURE 6. Histological section of the footpad. The ulcer margin is included (arrow) and there is full-thickness epidermal ulceration with erosion of the underlying dermis and colonization by bacteria and yeast in the area beneath the asterisk. *Inset*: Periodic acid–Schiff (PAS). High-magnification (×1200) detail of the area of ulceration below the asterisk, with clumps of mixed populations of bacteria and occasional broad-based budding "cottage-loaf" PAS-positive yeasts (*Malassezia* sp.) (arrow). No fungal hyphae are seen. Hematoxylin and eosin, scale bar 100 µm.

Fungal involvement was instead confirmed histologically through organism isolation and morphological identification from selective cultures of affected tissues.

Differential diagnoses for cranial mediastinal masses in ferrets can include neoplasia, mainly of lymphoid origin[16-18] and cryptococcal lymphadenitis.[6] Systemic coronavirus infection with development of a cranial mediastinal mass has also been recently reported.[19] Although no further tests were performed for coronavirus in the present case, there was no additional macroscopic or histological evidence to support the involvement of this virus.

The cause of concurrent erosive, ulcerative dermatitis confined to the footpads and external nares remained unclear. Possible etiologic explanations for the ulcerative dermatitis include vasculitis, thromboembolism, or ischemia of the extremities caused by angioinvasion by the fungus, leading to secondary colonization by mixed populations of bacteria and *Malassezia* sp. Evidence for these possible etiologic causes of the ulcerative dermatitis was not recognized in the peripheral blood vessels in the affected skin. It is also possible, although considered unlikely, that the ulcerative pododermatitis could have been a cause for the systemic candidiasis rather than a concurrent pathologic response. However, it was not possible to confirm either of these hypotheses. Paraneoplastic immune-mediated dermatoses associated with a number of tumors have been described in human and veterinary medicine.[20,21] Superficial necrolytic dermatitis is sometimes seen with glucagon-secreting pancreatic tumors in dogs and humans.[22,23] No evidence of neoplasia was identified by comprehensive postmortem examination in this case.

CDV can affect the respiratory tract, neural network, and dermis. Hyperkeratosis of the planum nasale and footpads often occur along with respiratory signs in ferrets infected with CDV. CDV infection should be suspected in unvaccinated ferrets with compatible clinical signs.[24] However, in this case, examination of multiple tissues by histology yielded no evidence of CDV infection. PCR results were consistent with the history of previous vaccination and excluded the possibility of both CDV and ADV involvement.

Unlike *C. albicans* and *C. tropicalis*, *C. parapsilosis* does not form true hyphae but exists either as yeast or as a pseudohyphal form.[25] It is widely distributed and has been isolated from humans, domestic animals, the marine environment, plants, and soil.[26,27] *C. parapsilosis* has emerged as a more

frequent cause of infections ranking from 15% to 25% of all the isolates from blood cultures in some hospitals worldwide,[12,28,29] and it is considered the most common commensal fungus isolated from the sublingual space of healthy volunteers.[30,31] Although less invasive into mucosal surfaces and vascular endothelia than other *Candida* spp.,[26] some of *C. parapsilosis* biological features, such as its morphological alterations, secretion of extracellular proteases, selective adherence, and formation of biofilms on plastic and prosthetic material (such as catheters or other implanted devices),[32,33] may explain persistence of this organism in hospital environments[25] and increased presence in severe human systemic infections[34-36] characterized by fever, septic shock, and renal failure.[37,38] Immunocompromised individuals are at high risk for developing invasive infections.[25] There are published reports that *Candida* spp. may become more prevalent in environments cohabited by people and animals.[39] *C. parapsilosis* is a reported cause of cutaneous and urinary tract infections in cats and dogs; abortion and mastitis in cattle; arthritis, endocarditis, and keratomycosis in horses; and alimentary tract infections in poultry.[40] Local proliferation of *Candida* spp. on mucosal surfaces or wounds is the initial step in the spread of infection. When immune defenses are compromised or normal intestinal, genital, or cutaneous microflora disrupted, *Candida* spp., which are normally commensals of the mucosal tissues of various domestic animals, act as opportunistic pathogens, invade deeper tissues, and proliferate or disseminate via the blood stream.[39]

Systemic fungal diseases are uncommon in the domestic ferret, but several cases have been described in the literature.[41,42] Concurrent underlying immunosuppression was suspected or mentioned in only a few of these cases.[42] *C. albicans* was isolated from a ferret with ulcerative skin disease. The same report mentioned that several cases of skin disease were associated with ADV in ferrets, suggesting that an impaired immune response may predispose these animals to nonspecific skin infections.[43] Immunodeficiency was also thought to be an influencing factor for the development of systemic candidiasis in a 4-month-old ferret from which *C. tropicalis* was isolated.[2] Most systemic mycotic infections in animals and humans are opportunistic and derived from the environment. Direct transmission of *Candida* spp. between animals and humans is rare, especially in immunocompetent individuals. Neither the origin of the infection nor any evidence of underlying immunosuppressive disease was identified in the ferret described in this report.

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