Microsporidian Keratoconjunctivitis in a Double Yellow-Headed Amazon Parrot (Amazona ochrocephala oratrix)

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Case Report

Microsporidian Keratoconjunctivitis in a Double Yellow-Headed Amazon Parrot (*Amazona ochrocephala oratrix*)

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Abstract: Microsporidian keratoconjunctivitis was diagnosed in the right eye of a young double yellow-headed Amazon parrot (*Amazona ochrocephala oratrix*). Previously, the bird's left eye had been enucleated because of fungal endophthalmitis. Clinical signs of the keratoconjunctivitis included corneal opacities and blepharospasm. Corneal scrapings demonstrated 1–2-μm, gram-positive organisms, and results of a corneal biopsy confirmed the presence of microsporidia. Treatment with oral albendazole and topical ophthalmic fumagillin was curative. Because animals can act as carriers of microsporidian organisms, we feel avian veterinarians need to be aware of this potential zoonotic concern.

Key words: keratoconjunctivitis, microsporidia, zoonosis, Amazon parrot, *Amazona ochrocephala oratrix*

Introduction

Microsporidia are obligate, intracellular, protozoal parasites characterized by the production of spores.[1] They are ubiquitous in nature and have been recognized to cause disease in both invertebrate and vertebrate hosts.[2] Over 100 genera and 1,000 species have been described.[3]

Microsporidian infections in invertebrates, such as silk worms, honeybees, and anopheline mosquitoes, have caused severe economic losses and the loss of research studies.[4] Infection in fish can also be widespread and inflict heavy mortality.[2] In laboratory rabbits and small rodents, microsporidian infections are common but are not always pathogenic. Infection is often found during routine histopathologic examination of tissues or by serologic testing in animals being studied for other reasons.[5]

Few cases of microsporidiosis in birds have been reported, and those reflect diagnoses based on necropsy findings. Common clinical signs reported before death include anorexia, lethargy, weakness, diarrhea, stunting, and weight loss. Microsporidiosis has been reported in blue-masked lovebirds (*Agapornis personata*),[6,7] peach-faced lovebirds (*Agapornis roseicollis*),[8–11] Fischer's lovebirds (*Agapornis fischeri*),[12] budgerigars (*Melopsittacus undulatus*),[13,14] and a yellow-crowned Amazon parrot (*Amazona ochrocephala*).[15] In cases of avian microsporidiosis where the organisms were identified, *Encephalitozoon* species were determined as the causative agent.

Microsporidian species that infect humans include *Encephalitozoon, Enterocytozoon, Vittaforma, Nosema, Pleistophora,* and *Microsporidium.*[16] Since the mid-1980s, cases of microsporidiosis in human patients with acquired immunodeficiency virus or other immunocompromising conditions have been reported with increasing frequency.[17–21] Clinical manifestations of microsporidiosis reported in human patients have included gastrointestinal disease, pneumonia, sinusitis, cystitis, myositis, and keratoconjunctivitis.

Diagnosis of microsporidian infection has been difficult because of the small size of the organism, the need for examination of thin histologic sections, the poor staining qualities of spores, and the lack

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of knowledge regarding clinical disease. Light microscopy with special stains, transmission electron microscopy (TEM), immunofluorescent staining, and polymerase chain reaction (PCR) probes are currently being used to identify microsporidian organisms.[16]

Treatment of microsporidiosis depends on the organ system(s) involved. In human patients, the most commonly recommended treatment is albendazole, with or without propamidine isethionate, and fumagillin.[17,22–24] In birds, no successful treatment has been reported.

In this report, we describe the presentation, diagnosis, and successful treatment of microsporidian keratoconjunctivitis in a double yellow-headed Amazon parrot (*Amazona ochrocephala oratrix*).

Case Report

A 3-month-old double yellow-headed Amazon parrot was referred for examination because of chronic conjunctivitis and sinusitis. The owner had purchased the bird at 10 days of age from a large aviary and had taken it to several bird fairs over the next several months. Details of the bird's history before purchase were unknown. A blood sample had been submitted by the referring veterinarian for a complete blood count (CBC), plasma biochemical analysis, and *Aspergillis* and chlamydial serologic testing before the conjunctivitis developed. Results of the serologic tests were negative, and those of the other tests were within reference ranges. The referring veterinarian had treated the bird with multiple topical and systemic antibiotics, but the clinical signs had not resolved.

On initial presentation, the bird was thin and weighed 343 g. In the left eye, the conjunctiva was hyperemic and the cornea appeared cloudy. Additionally, the eye was exophthalmic and blepharospastic. Further examination of the left eye with slit lamp biomicroscopy revealed mild corneal edema and hypopyon but no aqueous flare. A small white plaque, which was behind the nictitating membrane, was removed and submitted for cytologic examination. Structures posterior to the anterior chamber were not visible because of lesions of the anterior segment. The right eye was also examined, and results were unremarkable.

Cytologic examination of the plaque revealed branching septate fungal hyphae. A diagnosis of fungal keratoconjunctivitis with possible fungal endophthalmitis was made, and the bird was treated with natamycin (2 drops applied to the left eye q6h) (Natacyn®, Alcon Laboratories, Inc., Ft. Worth, TX, USA) and fluconazole (20 mg/kg per os [PO] q72h) (Diflucan®, Pfizer Roering, New York, NY, USA).

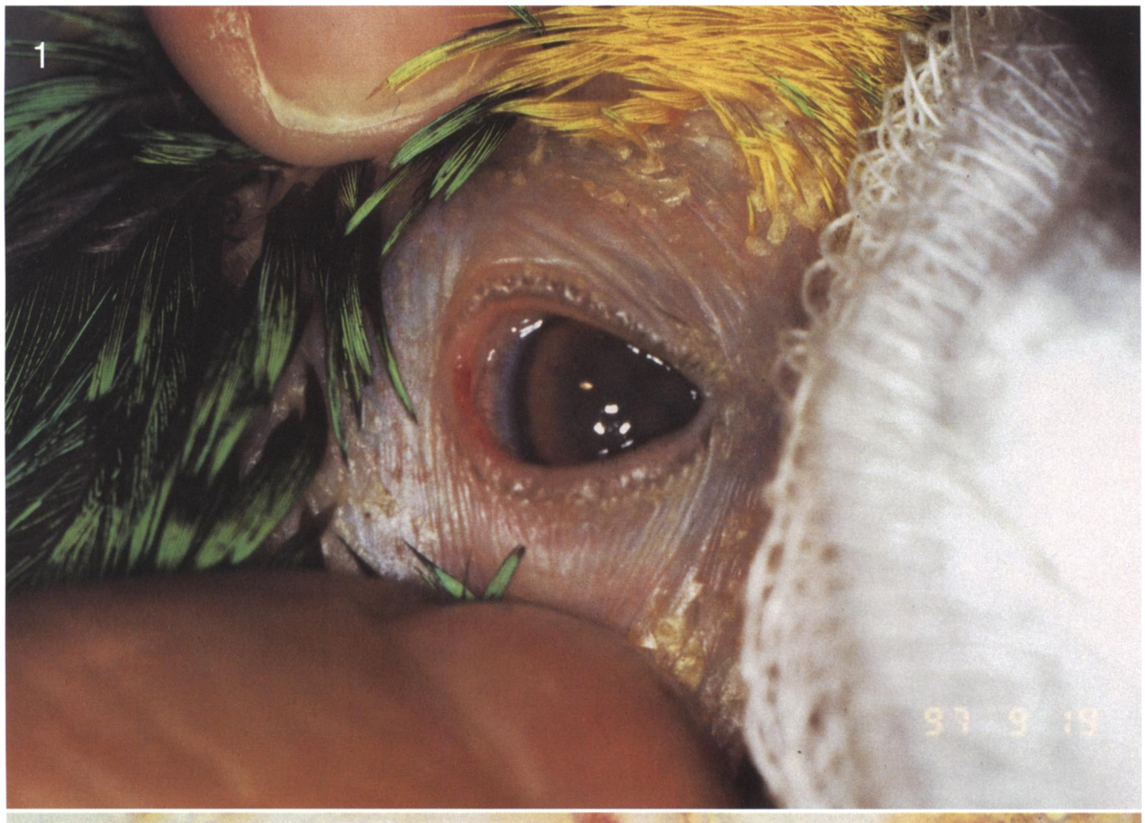
On examination 2 weeks later, the left anterior chamber was shallow. The right eye contained superficial corneal neovascularization overlying white opacities in the corneal stroma. The tentative diagnosis was fungal keratitis involving the right eye and fungal endophthalmitis of the left eye. Enucleation of the left eye was recommended. Treatment with natamycin was discontinued because of apparent lack of response, and therapy with miconazole was started (1 drop applied to the right eye [OD] q2h) (Monistat iv®, Janssen Pharmaceutica, Titusville, NJ, USA).

The left eye was enucleated by a subconjunctival approach. Histopathologic examination of the globe revealed a severe, subacute, diffuse pyogranulomatous keratitis and anterior uveitis accompanied by anterior synechia. Intralesional fungal hyphae were visible, but the species could not be identified. Treatment with miconazole was continued in the right eye. Fluconazole administration was discontinued and replaced with itraconazole (10 mg/kg PO q24h) (Sporanox®, Janssen Pharmaceutica) for systemic therapy of suspected aspergillosis.

After 1 week, the number of corneal opacities in the right eye had increased (Fig. 1). A blood sample was collected from the jugular vein for a CBC and plasma biochemical analysis. In addition, a corneal scraping sample was submitted for cytologic examination. The only abnormal finding in the CBC was a mild leukocytosis (14,400 cells/μl, reference range 5–12,500 cell/μl).[25] Results of the plasma biochemical analysis were within reference ranges.[25]

Cytologic examination of the corneal sample revealed hypocellularity with occasional bacteria and heterophils. Numerous small round gram-positive organisms, each with a small eccentric central dark body, were observed microscopically. Application of topical miconazole was discontinued, and the eye was medicated with triple antibiotic ophthalmic ointment (OD q8h) (TriOptic-P®, Pfizer Animal Health, Exton, PA, USA) and itraconazole (Janssen) compounded into an ophthalmic ointment[26] (OD q4h).

Six days later, a corneal biopsy was performed, and tissue samples were submitted for bacterial and fungal culture as well as cytologic and histopathologic examination. A blood sample was submitted for plasma biochemical analysis, protein electrophoresis, and *Aspergillis* serologic testing. Results of the plasma biochemical analysis were within reference range.[25] No globulinopathies were observed on the electrophoretogram, and the *Aspergillis* titer was negative for antibody but positive for antigen.



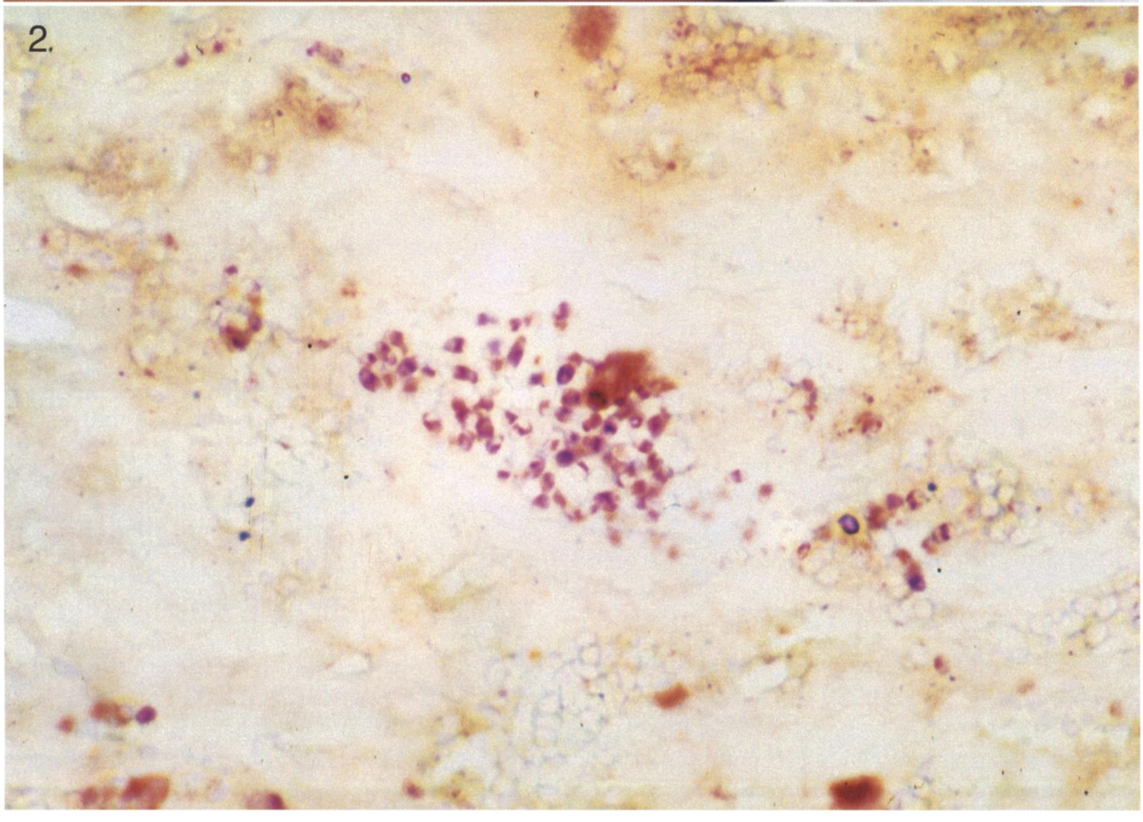


Figure 1. The right eye of a double yellow-headed Amazon parrot with corneal opacities caused by a microsporidian infection.

Figure 2. Photomicrograph of a corneal biopsy from the Amazon parrot described in Figure 1. The microsporidian organisms are gram-positive, oval structures visible here as the purple-staining structures. These spores were 1–2 μm in diameter. H&E stain. ×100.

Staphylococcus species was isolated from the bacterial culture, but no organisms grew on fungal culture. Cytologic and histopathologic examination of the corneal biopsy specimen revealed 1–2-μm gram-positive organisms with irregular nuclear structures consistent with microsporidian organisms (Fig. 2). The diagnosis was heterophilic microsporidian keratitis.

Triple antibiotic ointment therapy was continued after surgery. Treatment with oral itraconazole was continued because of the fungal hyphae observed previously in the left eye as well as the positive antigen result of the *Aspergillis* serologic test. Treatment initiated for microsporidian keratitis included albendazole (50 mg/kg PO q24h × 5 days) (Valbazen®, Smith Kline Beecham, Animal Health, West Chester, PA, USA) and fumagillin (1 drop OD q2h during the day) (Sigma Chemical, St. Louis, MO, USA).

To rule out immunosuppression predisposing the bird to secondary keratitis, samples were submitted for serologic tests for polyomavirus and psittacine beak and feather disease virus; results of both tests were negative. Histologic reevaluation of the enucleated left eye did not reveal microsporidian organisms.

Two weeks later, results of a CBC revealed a mild leukocytosis (14,800 cells/μl). Slight fluoroscein dye uptake was present at the previous biopsy site. Blepharospasm was less pronounced, but the white corneal opacities appeared unchanged. Treatment frequency with fumagillin was decreased (q8h), and albendazole was once again administered at the previous dosage (50 mg/kg PO q24h).

Urine, fecal, and serum samples were sent to the Division of Parasitic Diseases at the Centers for Disease Control (Atlanta, GA, USA) to attempt to identify microsporidian organisms. Polymerase chain reaction probes and special stains were negative for microsporidia. Plasma submitted for serologic testing cross-reacted in serologic tests (enzyme-linked immunosorbent assay and indirect fluorescent antibody assay) used in rodents for *Encephalitozoon* species. One month after the beginning of treatment, opacities appeared to be coalescing in the center of the cornea (Fig. 3). Results of a CBC revealed a mild leukocytosis (13,500 cells/μl). A fecal sample was collected and submitted for analysis; a small number of microsporidian organisms were evident on Gram's stain. Treatment with albendazole, fumagillin, and itraconazole was continued.

Results of a CBC repeated 6 weeks later revealed a low normal packed cell volume (40%).[25] Results of a fecal Gram's stain did not reveal microsporidian organisms. All treatments were continued.

On ophthalmic examination 3 weeks later, a dense white opacity was visible in the center of the cornea. The opacity was suspected to be scar tissue, but to rule out bacterial or fungal keratitis, a second corneal biopsy was recommended. After an additional 2 weeks of treatment, all medications were discontinued.

One week later, corneal and liver biopsy samples were collected for histopathologic examination. A section of each sample was sent to the Centers for Disease Control for analysis; results of PCR testing and special stains of the samples were negative for microsporidia. Histologically, the liver exhibited mild biliary hyperplasia and the cornea appeared normal. No microsporidians were seen in either organ. Triple antibiotic ophthalmic ointment was administered for 1 week after the corneal biopsy. One month after the biopsy was taken, the owner reported the bird showed no blepharospasm, ocular discharge, or change in corneal opacities (Fig. 4).

Discussion

To our knowledge, this is the first report of microsporidian keratoconjunctivitis in a parrot. The emergence of this condition in humans and the possible zoonotic potential of microsporidia make this disease important to avian clinicians.

Clinical microsporidian infections involving human patients are being reported more frequently, and microsporidiosis may become an important disease entity in avian species as well. The life cycle of microsporidia is direct and has two phases: a proliferative intracellular phase (merogony) and an infective stage in which spores are released into the environment (sporogony).[16] Once a microsporidian spore is ingested, favorable environmental stimulation, such as an appropriate pH, results in extrusion of a polar tube through which infective sporoplasm enters the host cell cytoplasm. Intracellularly, the sporoplasm divides into meronts, which continue to divide, pass through additional life stages, and mature into spores.[16] microsporidian spores appear to be highly resistant and may remain infective in the environment for months to years.[1,16]

Microsporidian spores have been found in feces, urine, and respiratory secretions, but the source of infection in most clinical cases in humans is unknown. An oral route of infection has been established experimentally.[2] In an outbreak in young budgerigars, fecal–oral transmission was suspected; morbidity and mortality rates decreased after husbandry changes prevented the birds from being in

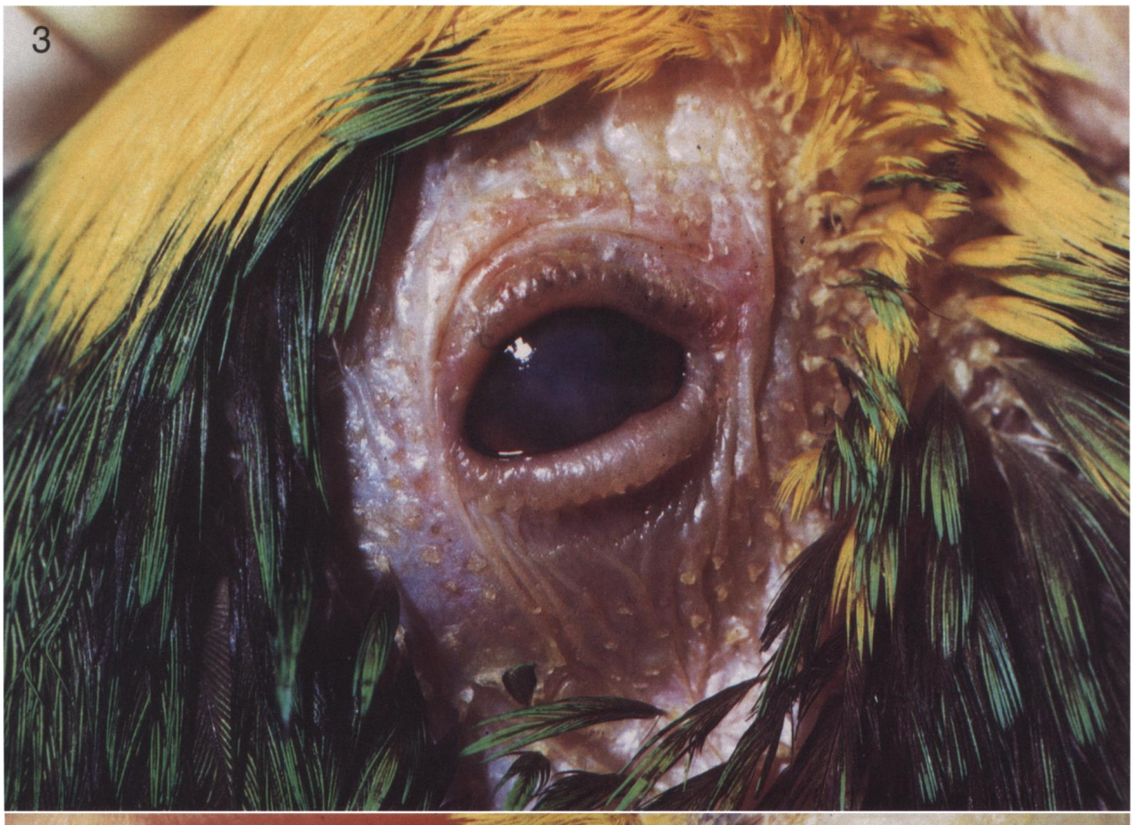


Figure 3. The right eye of the Amazon parrot described in Figure 1, 1 month after fumagillin and albendazole treatment for microsporidian keratoconjunctivitis was begun.

Figure 4. The right eye of the Amazon parrot described in Figure 1, 5 months after diagnosis of microsporidian keratoconjunctivitis and 1 month after treatment was discontinued. No evidence of any corneal opacity or blepharospasm was seen.

contact with feces at the cage bottom.[14] In carnivores, infection through predation and transplacental transmission has been reported.[2] Theoretically, animals may be a source of infection for humans.[27] One study reported that *Encephalitozoon cuniculi* identified in rabbits is zoonotic.[28] This suggestion was supported by a case of cerebral microsporidiosis in a human patient infected with the same strain of *E. cuniculi* isolated from rabbits in the area.[29] This patient also had contact with animals while living on a farm. In human patients with keratoconjunctivitis, autoinoculation is suspected from contaminated urine being deposited in the eye.[30]

In humans, fewer than 500 cases of microsporidiosis have been documented,[31] and most of these involved patients with human immunodeficiency virus or acquired immunodeficiency syndrome.[32] Symptoms reported in these individuals, depending on the organ system(s) involved, include chronic diarrhea, weight loss, neurologic signs, fever, bronchitis, pneumonia, sinusitis, and urethritis. Microsporidian keratoconjunctivitis has also been reported in humans, with symptoms including photophobia, foreign body sensation, ocular redness, and epiphora.[24,29,33,34] Punctate corneal erosions and opacities were also apparent. In confirmed cases, conjunctival scrapings revealed small gram-positive organisms presumed to be microsporidian organisms.

The blepharospasm, conjunctival hyperemia, and corneal opacities seen in the bird we describe are similar to the clinical signs seen in human cases. Cytologic examination of a corneal scraping in this parrot demonstrated gram-positive, round, 1–2-μm-diameter structures presumed to be microsporidian organisms. Microsporidian spores are the only gram-positive protozoal spores or cysts.[2] Histopathologic examination of the cornea confirmed heterophilic microsporidian keratitis.

Treatment of microsporidian keratoconjunctivitis in humans has consisted of fumagillin alone[30,34] or fumagillin in combination with albendazole.[24,33] In one report, systemic albendazole was administered after treatment with topical fumagillin.[33] Fumagillin is a derivative of *Aspergillus fumigatus* and was used initially by beekeepers to control *Nosema apis,* a microsporidian organism that infects honeybees.[35] The proposed mechanism of action of fumagillin involves inhibition of ribonucleic acid.[36] No adverse effects of fumagillin have been identified in humans.

Albendazole is a benzimidazole anthelmintic that has been used for disseminated microsporidiosis in humans. Although treatment protocols vary, albendazole is considered the treatment of choice for microsporidiosis.[17–19,37,38] Adverse effects of albendazole in humans include hepatotoxicity, neutropenia, and alopecia.[39] Serial CBCs and liver function tests have been recommended during treatment with albendazole.[33] In veterinary medicine, albendazole has been used primarily to treat endoparasites of cattle, sheep, goats, swine, cats, and dogs,[40] and it has been used occasionally to treat nematodiasis in birds. Suspected albendazole toxicosis has been reported in keas (*Nestor notabilis*), southern speckled pigeons (*Columba guinea phaenota*), and pink spotted fruit doves (*Ptilinopus perlatus perlatus*).[41] All affected birds were given doses of albendazole ranging between 50 and 100 mg/kg. Clinical signs associated with toxicosis include weight loss, leukopenia with marked heteropenia, and bone marrow depletion. No adverse effects of treatment with albendazole were seen in the Amazon parrot we describe, despite a treatment period of 3 months.

The gold standard for identifying microsporidian organisms has been TEM. With the use of TEM, species have been identified by the number of turns of the polar tube, although other methods of diagnosis have been described.[3,16,24] Most recently, PCR methods and Southern blot analysis have been used to identify microsporidian organisms.[14] In birds, microsporidian species have been identified by electron microscopy. Unfortunately in this case, no corneal tissue remained from the biopsy sample to submit for electron microscopy. Negative PCR and special stain results were likely a result of our initiating treatment before sample submission.

Gram's staining of conjunctival scrapings has been used as a diagnostic test for microsporidiosis in human cases of keratoconjunctivitis; this technique may be useful in birds demonstrating similar clinical signs. However, the microsporidian species cannot be identified on a Gram's-stained specimen.

Previous reports of avian microsporidian infections did not describe lesions associated with the eye or orbit. Hepatic necrosis is the most common necropsy finding,[6,7,9–11,14] although biliary hyperplasia, enteritis, and nephritis have been described as well.[6,7,10–12,15] A biopsy sample from the liver of this Amazon parrot was submitted after treatment was begun. On histologic examination, no evidence of protozoal hepatopathy was apparent, but biliary hyperplasia was observed. This might suggest that the liver was infected but responded to treatment.[7,9,12]

Immune suppression was suspected but not specifically determined in this bird. Severe secondary infections such as microsporidiosis in human patients are most common with immunosuppressive conditions, especially human immunodeficiency virus. This parrot tested negative for both polyoma-

virus and psittacine beak and feather disease virus. Overwhelming viral infections can often result in leukopenia,[25] but in this parrot, the white blood cell count remained stable. The fungal endophthalmitis diagnosed in the left eye may have contributed to, or was a manifestation of, immunosuppression. Other potentially stressful events that could have weakened the bird's immune system included travel and change in ownership, chronic medical therapy with multiple antibiotics, and weaning. Unfortunately, limited information was available regarding details of hatching, aviary location, feeding habits, handling, and travel. In reported cases of avian microsporidiosis that noted age, affected birds were 7 months or younger.[10,11,13,14]

Because of the increasing awareness of microsporidian infections that affect humans, as well as the availability of diagnostic tests that are technologically advanced, microsporidian infections may soon be more commonly diagnosed in birds. The potential of birds, and other animals, acting as zoonotic carriers of microsporidian organisms requires further investigation. Although microsporidiosis has not yet been proved as a zoonotic disease, avian veterinarians should be aware of this potential risk.

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