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Source: Journal of Avian Medicine and Surgery, 36(3) : 295-301

Published By: Association of Avian Veterinarians

URL: https://doi.org/10.1647/21-00048

Journal of Avian Medicine and Surgery 36(3):295–301, 2022

Clinical Report

Medical and Surgical Management of Phaeohyphomycosis in a Kea (*Nestor notabilis*)

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Abstract: A 2.5-year-old female kea (*Nestor notabilis*) weighing 711 g was presented for acute lethargy, pelvic limb paraparesis, and decreased appetite. Results from a complete blood count revealed a leukocytosis (67540 cells/μL [reference interval 4200 – 37880 cells/μL]). Radiographic images revealed a mass effect within the mid coelom. The patient was provided supportive care that included antifungal medication (voriconazole 15 mg/kg PO q12h x 6 months and 10 days) and antibiotic therapy (enrofloxacin 20 mg/kg PO q12h x 27 days). A discrete 2.3 × 2.7 × 2.6 cm soft tissue mass adjacent to multiple organs was identified on contrast computed tomographic images (IsoVue 370 at 4 mL/kg IV over 2 minutes). The mass was medial and dorsal to the proventriculus, cranial to the ventriculus, caudal to the liver, and ventral to the cranial renal divisions. The mass had an irregular vascularized wall with a poorly vascularized center. Ten days after initial presentation, exploratory coeliotomy and mass removal via left lateral coeliotomy were performed. Bacterial (aerobic and anaerobic) and fungal cultures were negative. Fourteen days postsurgery, the leukocytosis was resolved. Microscopic review of the submitted tissue mass found multinucleated giant cells, macrophages, and brown fungal hyphae with irregular internal septations and some branching, leading to a diagnosis of phaeohyphomycosis. Panfungal polymerase chain reaction testing and sequencing were unsuccessful at speciation. Treatment with voriconazole was continued until behavioral, hematologic, and computed tomographic assessments indicated resolution of the problem 6 months postsurgery. No recurrence of disease has been reported 20 months following mass removal.

Key words: Nestor notabilis, kea, avian, phaeohyphomycosis, granuloma, surgery, computed tomography

CLINICAL REPORT

A 2.5-year-old female kea (*Nestor notabilis*) weighing 711 g and with a body condition score of 3/5[1] was presented to the Parrish Creek Veterinary Hospital and Diagnostic Center (Centerville, UT, USA) for acute abnormal behavior on the same day. The patient was observed to be laying on her sternum with her head resting on the ground and wings splayed out. The patient was acting lethargic, tripping over perches and toys, disinterested in treats, and running into the normal holding cage walls. Prior to this event, the patient was observed eating and interacting normally within its enclosure. The patient was received from another facility 1.5 years earlier as a hand-reared bird.

The kea lived in a 158 square meter public outdoor enclosure with indoor holding. Both areas had a variety of natural perching and platforms. The exhibit was filled with non-destructible synthetic, destructible natural, and foraging toys. The diet consisted of 70% pellets (Lafeber Macaw Pellets, Lafeber Company, Cornell, IL, USA), vegetables, fruits, and a small portion of tree nuts. There were 2 male keas on exhibit with the female, but no other female adult keas or other avian species on exhibit. All birds were examined yearly

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and had a complete blood count (CBC), biochemistry panel, and *Chlamydia psittaci* test performed as part of the examination. The *C. psittaci* testing was done using polymerase chain reaction testing from conjunctival, choanal, cloacal, and blood samples based on the diagnostic laboratory's recommendation. Within the same exhibit, no other birds were reported as abnormal from the time the patient presented to cessation of treatment.

At the time of the physical examination, the patient was quiet, alert, and responsive. While the kea was perching and moving during the examination, it was also observed to have a stumbling gait when trying to avoid restraint. The patient's grip strength was decreased bilaterally, with the right leg being weaker; hyporeflexia was also noted bilaterally. These abnormalities were consistent with a lower motor neuron process. Muscular tone, postural reaction, cranial nerve reflexes, superficial pain, and deep pain were found to be normal on the remainder of the neurologic exam. All other physical examination findings were normal.

Initial diagnostic testing performed at the time of presentation for this patient included a CBC, biochemistry panel, and radiographic images. A blood sample was collected from the right jugular vein for the CBC (Eopette, Exotic Animal Solutions LLC, Rockledge, FL, USA) and biochemistry panel (VetScan Avian Reptile Profile Plus, Abaxis, Union City, CA, USA). The only abnormal value from the blood tests was a significant leukocytosis (67500 cells/μL, reference interval 4200 – 37900 cells/μL).[2] With the patient conscious, radiographic images were obtained (standard orthogonal views; I-Vision CR, IDEXX, Memphis, TN, USA). On the lateral view, the abdominal and caudal thoracic air sac spaces were compressed by an irregular 2.8 × 2.1 cm sized soft tissue radiodense mass. The mass was dorsal to the aborad proventriculus and isthmus, orad ventriculus, and cranioventral to the cranial renal divisions. The caudal border of the mass effect was questionable due to summation (Fig 1A). The hepato-intestinal silhouette was bilaterally widened on the ventrodorsal radiograph when the boundaries of the scapulohumeral to coxofemoral regions were traced; the mass was not easily discernable due to summation (Fig 1B). Based on the diagnostic test results, the patient was prescribed enrofloxacin (20 mg/kg PO, q12h x 27days; Enrofloxacin, MedsforVets LLC, Sandy, UT, USA), voriconazole (15 mg/kg PO, q12h x 6 months 10 days; Voriconazole, MedsforVets LLC), and 0.9% NaCl (50 mL/kg SQ, q24h x 10

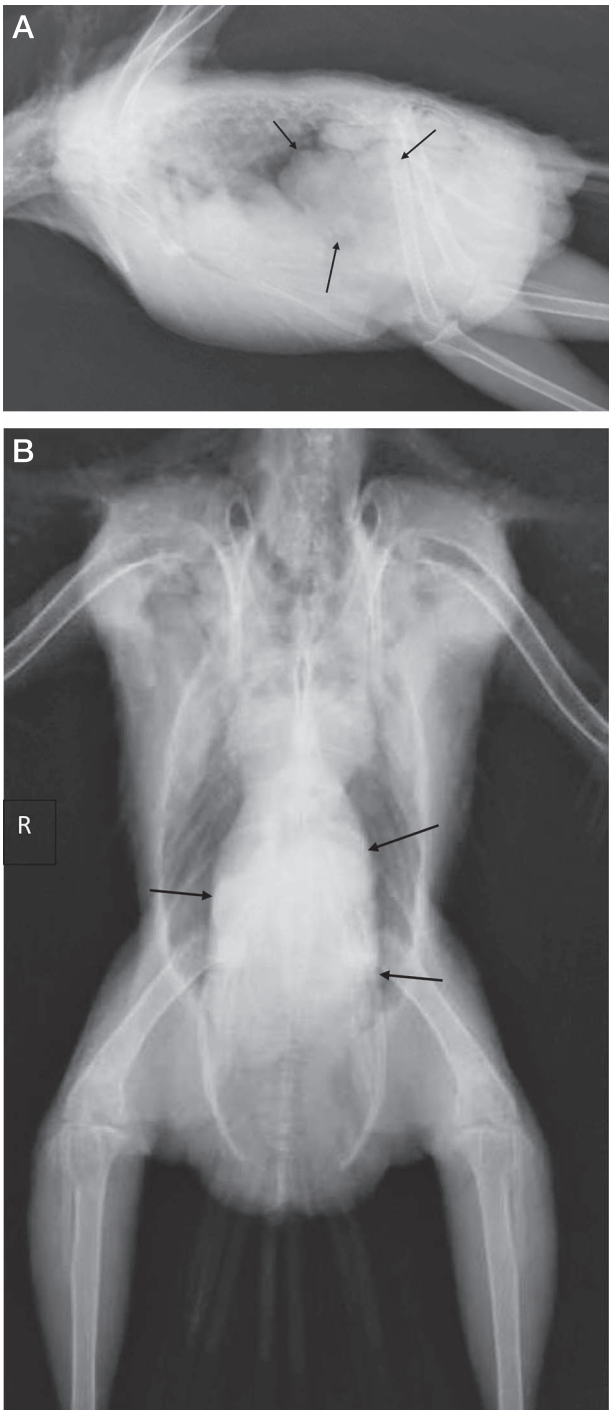

Figure 1. Right lateral (A) and ventrodorsal (B) projection radiographs of a 2.5-year-old female kea (*Nestor notabilis*) that was presented for acute lethargy, pelvic limb paraparesis, and decreased appetite. Both images show a loss of the abdominal and caudal thoracic air sac space due to a mid-coelomic mass effect (black arrows), diagnosed as a phaeohyphomycotic granuloma.

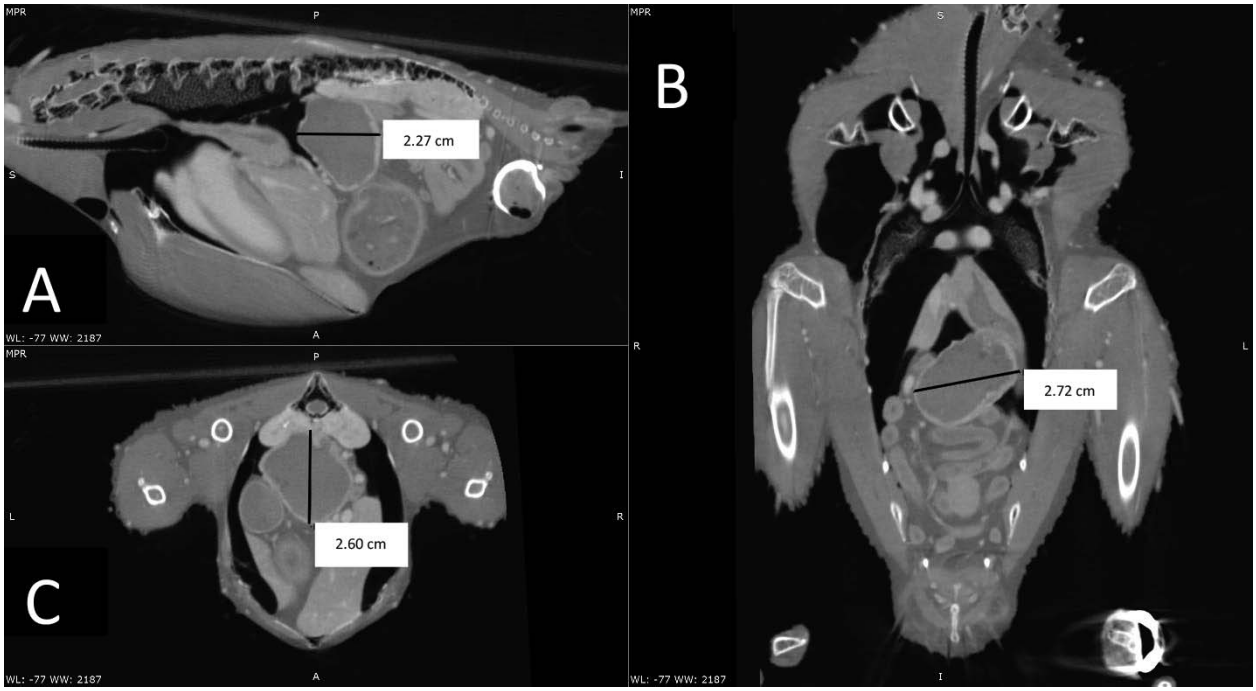

Figure 2. Computed tomographic scans of the 2.5-year-old female kea (*Nestor notabilis*) described in Figure 1 showing the during-contrast scan at 200 μm slices, mA 60, kVp 80, and exposure time 7 milliseconds. The scan represents (A) the sagittal, (B) coronal, and (C) axial planes of approximately the same location. The soft tissue mass measured 2.27 × 2.72 × 2.60 cm in size as indicated by the black lines in each figure, and also provides visualization of the poorly vascularized center of the mass.

days; Sodium chloride 0.9%, Baxter, Deerfield, IL, USA).[3] Four days after initial presentation, the patient was no longer eating on its own and nutritional support (30 mL/kg PO, q12h x 24 days; EmerAid Omnivore, Lafeber Company) was initiated.

Five days after initial presentation, a whole body computed tomographic (CT) (Epica Vimago, Epica Animal Health, San Clemente, CA, USA) scan at 200 μm slice thickness, mA 60, kVp 80, and exposure time of 7 seconds was performed on the kea while it was under general anesthesia and in dorsal recumbency. The patient was bright and alert, but still had stumbling, poor grip strength, and leg weakness as previously noted. The kea was pre-medicated with butorphanol (2 mg/kg IM; Torbugesic 10 mg/mL, Zoetis, Kalamazoo, MI, USA) and general anesthesia was induced with isoflurane at 5% in 95–100% oxygen administered by facemask at 2 L/min. The patient was intubated with a 4 mm uncuffed endotracheal tube (Surgivet AT40 endotracheal tube; Smith's Medical, Dublin, OH, USA). Anesthesia was maintained at 2–3% isoflurane using the same oxygen flow rate as induction. An intravenous catheter (25-gauge Catheter, Sur-Vet TERMO, Laguna Techno Park, Binan, Laguna, Philippines) was placed within the left basilic vein. Three scans were performed: 'no contrast'; 'during contrast', where the scan was initiated after 30 seconds into a 2-minute infusion of 4 mL/kg of 370 mg/mL iodinated contrast agent (Iopamidol, IsoVue-370; Bracco Diagnostics Inc, Milano, Italy); and a 'post-contrast' scan after the 'during contrast scan' was completed, which was approximately 4 minutes after initiation of contrast agent administration. [4,5] Following the CT scan, the patient recovered uneventfully from anesthesia.

On all three scans, a soft tissue dense mass was found measuring 2.3 × 2.7 × 2.6 cm and located medial and dorsal to the proventriculus as well as pressing upon the proventriculus, cranial to the ventriculus with no deformation of the ventriculus, caudal to the liver and adjacent to the right hepatic lobe ventrally, and ventral to the cranial renal division (Figs 2A and 2B). The dorsal aspect of the mass appeared to originate adjacent to the location of the left ovary, which was not visible, and was directly ventral to the left common iliac vein. The mass wall or capsule was not differentiated from the left cranial renal division. At 2 points, the mass pressed dorsally into the renal parenchyma and appeared to be separate and distinct from the other adjacent organs. The mass had a thin irregular vascularized wall, and for the most part a poorly

vascularized center. The cranial aspect of the mass was somewhat compartmentalized with different vascular regions. At this time, the differential disease diagnoses for the mass included granuloma, abscess, or neoplasia of the gastrointestinal tract, reproductive organs, or adrenal glands. Also noted were increased amounts of intracoelomic and subcutaneous fat, consistent with an increased body condition score of 4/5.[1] This was attributed to better visualization of fat in comparison to that identified on the external physical examination.

Due to the possibility of a reproductive origin of the mass, and the high reproductive value of the individual, the patient was given 1 injection of leuprolide acetate (400 μg/kg IM; Lupron Depot, Lupron Depot 1000 μg/mL, AbbVie Inc, North Chicago, IL, USA). The patient was switched to lactated Ringer's solution (25 mL/kg SQ, q12h x 14 days; Lactated Ringer's solution, Dechra, Overland Park, KS, USA) and continued with gavage feedings at 3% body weight as needed when the patient was not observed eating, enrofloxacin, and voriconazole. Meloxicam (1.6 mg/kg PO, q12h x 14days; Metacam 1.5 mg/mL, Boehringer Ingelheim, St. Joseph, MO, USA) was also initiated at this time. Surgical exploration to identify and possibly remove the mass was planned for 5 days later.

Ten days after initial presentation, the patient was prepared for an exploratory coeliotomy. A pre-surgical CBC was performed, and the only abnormality identified was a continued leukocytosis (55700 cells/μL). The patient was pre-medicated, induced, and maintained for anesthesia as previously described. The patient was placed in right lateral recumbency, with the right leg positioned caudally and the left leg positioned cranially; this allowed for a left flank approach, which was determined to be the most direct approach based on the CT scan. A 25-gauge intravenous catheter was placed within the right basilic vein as previously described. Intravenous 0.9% NaCl (10 mL/kg/hr) was administered for the duration of the procedure. Intermittent positive pressure ventilation was performed at 6-8 breaths per minute initially, then at 8-12 breaths per minute after the intestinal peritoneal cavity was incised and caudal thoracic and abdominal air sacs were exposed. Monitoring was performed with stethoscope auscultation and an ultrasonic Doppler pulse monitor (Ultrasonic Doppler Flow Detector Model 811-B, Parks Medical Electronics Inc, Aloha, OR, USA) at the level of the carpus. Indirect blood pressure was monitored throughout the procedure with a size 2 blood pressure cuff (Sharn Blood Pressure Cuff, Sharn Anesthesia Inc, Caledonia, MI, USA) placed around the humerus and sphygmomanometer (ri-san sphygmomanometer, Rudolf Riester GmbH, Jungingen, Germany). Systolic blood pressure was recorded every 5 minutes using the ultrasonic Doppler pulse monitor. Thermal support was provided with a warm water-recirculating pad (T/Pump Heat Therapy Model No. TP-400, Gaymar Industries Inc, Orchard Park, NY, USA) and overhead heat lamp (E191381 Work Light 43 MK, Utilitech Inc, Cincinnati, OH, USA). The patient maintained normal vital signs throughout the procedure. There was minimal blood loss during the procedure, and a total of 13.6 mL of 0.9% NaCl was administered during the surgery.

Feathers from the left lateral and caudal aspect of the coelomic skin were plucked. This region was isolated and sterility maintained from the surrounding feathers using white medical tape (Covidien, Mansfield, MA, USA). Following preparation of the surgical site, a large clear fenestrated drape (Veterinary Transparent Drape, VSP, Mission, KS, USA) was applied over the surgical site. Magnification loupes (Front Lens Mounted Compact, 5.5x, Surgitel, Ann Arbor, MI, USA) were used throughout the procedure. A 2.5-3 cm skin incision was made with microsurgical scissors (Microsurgical scissors, 2602-105, Sontec Instruments, Centennial, CO, USA) at the level of the left flank using the cranial border of the pubis to the uncinate process of the last rib as landmarks, then freed from underlying tissue by blunt dissection. In the paralumbar fossa, 3 layers of lateral coelomic musculature, the external oblique, internal oblique, and transversus abdominus, were incised individually at the muscle-aponeurosis junctions. For visualization of the mass, 0.75 cm of the left caudal most rib was excised. The intestinal peritoneal cavity was explored and a dark purple to black mass was located in the area previously identified on the CT scans. There were multiple adhesions to the dorsal, medial, and medial ventral surfaces of the mass. The lateral aspect of the mass was freed from the adhesions. The dorsal adhesions were bluntly dissected with no apparent effect on the kidney. Most of the substantial adhesions were associated with the dorsolateral aspect of the proventriculus and surrounding fat. One medium hemostatic clip (Teleflex Medical, Research Triangle Park, NC, USA) was placed between the mass and the proventriculus to control hemostasis and effectively separated the mass from its main blood supply, a branch of the cranial mesenteric artery.

Blunt dissection and tissue clamping, followed by sharp dissection, were used to excise the mass. A small inactive ovary was noted during the exploratory coeliotomy. The remaining visible viscera were grossly normal. The muscular layers were closed individually with polydioxanone (4-0 One Dox, VetOne, MWI, Boise, ID, USA) in a simple interrupted pattern. The subcutis was also closed with 4-0 polydioxanone in a simple continuous pattern, while the skin was closed with 4-0 polydioxanone in an interrupted horizontal mattress pattern. Isoflurane anesthesia was discontinued, and the non-rebreather system was flushed of all gas anesthetic. The patient recovered uneventfully and was observed post-operatively until she was alert enough to stand. Total anesthetic time was 2 hours, and surgical time was 1.5 hours. The patient was then returned to the carrier and observed standing normally prior to returning her to the collection for continued care at the client's hospital facility.

A post-operative packed cell volume and total solids found a mild decrease in the packed cell volume from 38 to 32%. Post-operative butorphanol (2 mg/kg IM) was administered. The patient was continued on meloxicam (1.6 mg/kg PO, q12h x 14days), enrofloxacin (20 mg/kg PO, q12h x 14 days), and voriconazole (15 mg/kg PO, q12h x 6 months 10 days). Over the next 14 days, the kea had a decreased appetite but was provided nutritional support with the previously described supplemental oral feeding formula (30 mL/kg PO, q12h).

Once the patient recovered and returned to its facility, the mass was examined. Multiple samples of the mass were submitted for diagnostic testing that included cytology, aerobic and anaerobic bacterial culture, fungal culture, and histology. The impression smear of the mass was stained with Wright-Giemsa stain (Wright-Giemsa stain, Rapid Differential Stain, VetOne, MWI, Meridian, ID, USA) and the cytological report stated that the sample contained red blood cells, an abundant mixed white blood cell population, and numerous pigmented septated branching fungal hyphae. Cultures from the mass were all negative. Histopathology of the mass revealed granular material, cell debris, and fibrin. There were, in some areas, a border of multinucleated giant cells and macrophages. In some sections, there were large numbers of pigmented fungi. These fungal hyphae were brown with irregular internal septations and some branching (Fig 3). The final histopathological diagnosis was fungal granuloma, and more specifically phaeohyphomycosis based on the histologic

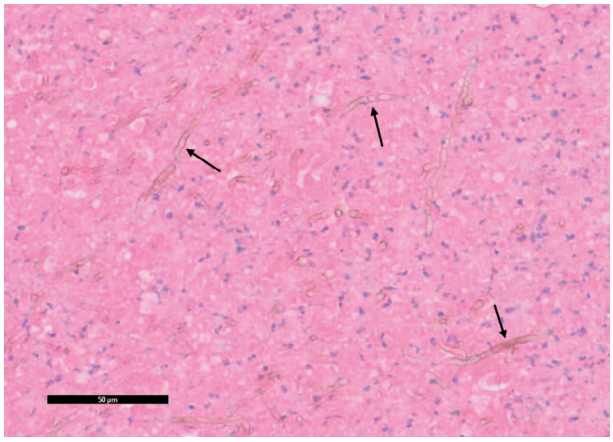

Figure 3. Histopathologic findings from a coelomic mass surgically removed from the 2.5-year-old kea (*Nestor notabilis*) described in Figure 1. Photomicrograph of the mass with large numbers of brown-pigmented fungi that have irregular internal septa and branching hyphae (black arrows); the fungi are dispersed within fibrin and debris (hematoxylin and eosin, x400).

functional morphology. Nutritional support, meloxicam, and enrofloxacin were discontinued 14 days following the surgical procedure based on diagnostic test results and clinical improvement of the patient.

Forty-three days after the kea's initial presentation, the patient was presented for a follow-up examination, CBC, and biochemistry panel. The bird was reported to be normal on exhibit and was observed to have normal appetite. There were no abnormalities noted on the physical examination, CBC, or biochemistry panel.

Six months and 10 days after the kea's initial presentation, the patient was presented for a CBC and a CT scan. The patient was reported to be exhibiting normal behavior in its exhibit at the time of this visit. There were no abnormalities noted in the CBC results. The recheck CT scan showed no evidence of granuloma formation at the site of the mass removal. At this time, the voriconazole was discontinued and a CBC was scheduled for 15 days later. Fifteen days after discontinuing the voriconazole, the CBC was found to be unremarkable.

One year after initial presentation, a physical examination, CBC, biochemistry panel, and CT scan were performed. No abnormalities were found on the physical examination, CBC, or biochemistry panel. The CT images showed no evidence of granuloma regrowth or mass development at a new location.

Twenty months following the surgical procedure, the patient was doing well and there were no signs of disease recurrence. Multiple attempts have

been made to speciate the causative organism past the classification of phaeohyphomycosis, but none have yielded a definitive diagnosis. These attempts included unsuccessful panfungal PCR and sequencing at the Texas A&M Veterinary Diagnostic Laboratory (College Station, TX, USA). Unfortunately, there are no specific serologic or antigenic tests available for this pathogen.

DISCUSSION

This report describes a case of phaeohyphomycosis in a kea. Based on an extensive literature review, this is the first case of antemortem diagnosis and successful treatment of phaeohyphomycotic granuloma in an avian patient, as well as the first case of phaeohyphomycosis described in a psittacine. The primary physical examination findings were abnormal mentation and lower motor neuron disease affecting the legs bilaterally. Computed tomographic imaging revealed a mass within the mid dorsal coelomic cavity. Surgical removal of the mass was successful, and histopathological evaluation of the submitted mass led to a definitive diagnosis of phaeohyphomycotic granuloma. Short-term supportive care and long term antifungal therapy following surgery resulted in the clinical resolution of disease in this patient.

Phaeohyphomycosis is caused by a group of dematiaceous fungi (70 genera and 150 species), which are saprophytic molds containing dark pigments (usually melanin) localized in the cell wall of the organism.[6] While black fungus *Chaetothyriales* is absent in birds, members of *Ochroconiales* have repeatedly been reported in chickens (*Gallus gallus domesticus*), turkeys (*Meleagris gallopavo*), grey-winged trumpeters (*Psophia crepitans*), quail chicks (*Coturnix* species), and snowy owl chicks (*Nyctea scandiaca*).[7–10]

Phaeohyphomycosis has been reported in mammals and birds; however, unlike in mammals, most avian cases are described as central neurologic disease.[7–9,11–13] Phaeohyphomycosis can affect both immunocompetent and immunocompromised patients, but immunocompromised individuals are still considered to be at a greater risk of infection.[7,11,12] These dematiaceous fungi are known to grow near hot spring effluents, thermal soils, and self-heated coal waste piles.[8] Most infections of other phaeohyphomycotic species occur sporadically in wild birds maintained in captivity, but at times occur in poultry facilities.[6] *Ochroconis gallopava* is a thermotolerant dematiaceous fungus that causes subcutaneous and systemic mycosis in poultry and other birds.[7,10,14–17] Significant neurotropic potential of phaeohyphomycosis has been described in turkeys (*Meleagris gallopavo*) less than one-year-old.[7,15,16,18] Culture of dematiaceous fungi is difficult on standard media and may require special culture media.[9]

In a snowy owl chick with *Dactylaria constricta* var. *gallopava*, the bird showed an acute onset of unusual neurological signs.[10] The clinical signs exhibited by the snowy owl included sudden development of ataxia, severe intermittent torticollis, and rigidity of the legs with repeated rocking backward to the point of falling over. All of these signs were attributed to widespread encephalitis.[10] Although there is a report of mycetoma in a grand eclectus (*Eclectus roratus roratus*) with neurologic disease, the fungus was not classified as phaeohyphomycosis.[19] Due to the changes in nomenclature associated with this disease process, future work should be performed to better classify previous findings.[9]

There is no standard of therapy for phaeohyphomycosis in avian medicine. In one American human medical review, a combination of amphotericin B, 5-fluorocytosine, and itraconazole were associated with improved survival; however, the results of the study were based on a low number of cases and should be used with caution.[12] There are species of dematiaceous fungi that are resistant to *in vitro* amphotericin B, which is often used as the reference standard of phaeohyphomycosis treatment.[20] Among available pharmaceutical agents, itraconazole and voriconazole have the most consistent results against phaeohyphomycotic organisms.[21] A review of phaeohyphomycotic disease by the European Society of Clinical Microbiology and Infectious Diseases and the European Confederation of Medical Mycology found that, depending on the genus of the organism and the clinical manifestation of infection, the recommended antifungal medications differ.[13] The report also suggested the addition of terbinafine to any antifungal therapy regimen to treat this fungus.[13] In the present case, voriconazole and surgical removal of the granuloma led to a positive outcome. Unfortunately, sensitivity of the fungus to voriconazole could not be verified because the fungus was not isolated in culture. The lack of success in further characterizing the organism by molecular testing was attributed to the formalin.

Historically, this bird was exposed to an outdoor enclosure that may have contained the phaeohyphomycotic organism. The authors suspect that this kea was opportunistically infected via inhalation, and that the granuloma formed over time.

Due to the unique nature and lack of peer-reviewed literature regarding phaeohyphomycosis in psittacines, 3 parameters were set to determine resolution of the disease process. The first was to return the bird to its normal behavior, appetite, and mentation. The second was serial CBCs to evaluate the bird's treatment response relative to the significant leukocytosis identified upon presentation, with the goal of 2 normal leukocyte counts indicating hematologic resolution. The final parameter was CT confirmation of no regrowth. The first was achieved at 13 days, the second at 1 month, and the third at 6 months postsurgery. Due to the rapid resolution of clinical signs and the leukocytosis, surgical removal was determined to be curative in this case.

While phaeohyphomycosis has been described in the literature, this is the first report of successful antemortem diagnosis and treatment of a phaeohyphomycotic granuloma in an avian patient. Although *Aspergillus* species is commonly diagnosed and reported as the source of fungal granulomas in avian species, other mycotic organisms should be considered.

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