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Diagnostic Techniques and Interventions Applied to Treat the Associated Disease

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Abstract

Mycotic nasal cavity and paranasal sinus infections in non-human primates (NHPs) are relatively uncommon diseases of the upper respiratory tract. This case study describes the clinical and pathological features. A 23-year-old primiparous female Sumatran orangutan residing at Perth Zoo in Western Australia developed intermittent episodes of right-sided epistaxis. An ulcerative nasal mass was identified from a diagnostic endoscopy. The mass was initially biopsied and showed the morphological characteristics of a dematiaceous fungal organism upon a histological examination. There were prominent mucosal and sub-mucosal granulomatous infiltrates containing histocytes, giant cells and lymphocytes admixed with fewer numbers of neutrophils and eosinophils surrounding the fungal organism. The organism was identified as *Curvularia sp.* by the fungal characteristics associated with the histopathology, culture growth and PCR analysis. The mass was subsequently removed with endoscopic sinus surgery (ESS) and the orangutan was medically treated with itraconazole for several months. The recovery was uneventful and the orangutan returned to full health.

Keywords: *Curvularia sp.* • Rhinosinusitis • Endoscopic sinus surgery • Orang-utan

Introduction

An infection of the respiratory tract in non-human primates (NHPs) can be a common manifestation of disease within this group. The disease can be described by either the infectious agents such as viruses, bacteria, parasites, or fungi or by the anatomical location of the disease, i.e., the upper and lower respiratory system. Often, both the infectious agent and the location of infection are used in concert to present the most accurate description of the disease and disease process.

Although the anatomical demarcation between the upper and lower respiratory tract can vary [1], in general the upper respiratory tract (URT) in NHPs is broadly similar to humans even though orangutans lack a frontal sinus [2]. The anatomy of the URT includes all extrapulmonary structures described in humans; namely, the nasal cavity, sinuses, nasopharynx, trachea, larynx and large bronchi [3]. In addition, various species of great apes and old-world monkeys also have well-developed laryngeal diverticula (i.e., air sacs), which are vestigial structures in humans [4]. The lower respiratory tract consists of structures not part of the URT and this can include smaller bronchi and bronchioles as well as alveoli with the lung parenchyma. The URT is a common site of infection in NHPs and, as with humans, can be associated with a wide variety of pathogens. Infections can occur in all structures of the upper and lower respiratory system, but the air sacs and nasal cavity have a noticeably high incidence of disease in NHPs [5-7].

Viruses and bacteria are commonly associated with respiratory system diseases in NHPs and can include a wide variety of agents [3,6,8]. Mycotic infections, on the other hand, are less common, but can cause severe disease. In NHPs, Pneumocystis sp. and dimorphic fungi appear to be common fungal agents of URT disease. It seems reasonable to infer that respiratory disease caused by other primary or opportunistic fungal pathogens could also induce significant URT disease in NHPs and should be considered to be a potential cause of clinical disease. This case report describes an incident of a nasal and paranasal sinus infection associated with *Curvularia*, a dematiaceous fungus in an orangutan. Although *Curvularia sp.* is noted to be an emerging pathogen in humans (causing phaeohyphomycosis as well as chronic mycotic rhinosinusitis), this fungus has not been previously documented to have an infectious etiology in NHPs. Accordingly, to the best knowledge of the authors and this is the first reported incidence of fungal rhinosinusitis caused by *Curvularia sp.* in an NHP.

Case Study

An otherwise healthy 23-year-old primiparous female Sumatran orangutan (*Pongo abelii*) at Perth Zoo in Western Australia developed intermittent unilateral epistaxis from the right nostril over several weeks. The orangutan was housed with her daughter in a 190 m^2 enclosure with daily outdoor access. Her diet included a daily provision of fresh produce (vegetables, leafy greens, fruit and nuts); a custom-made primate pellet with varied protein sources, including egg, quinoa and sardines; and locally sourced plant material that included *Ficus, Coprosma and* banana leaves.

To investigate the cause of the epistaxis, the orangutan underwent a diagnostic endoscopic procedure. This procedure was performed under general anesthesia and, as such, the orangutan was fasted from solid food for eight hours and oral fluids for one hour prior to the surgery. The orangutan was premedicated with 1.5 mg alprazolam per os and then, after 60 min, was administered 2.3 mg/kg of 100 mg/mL tiletamine and zolazepam (Zoletil®, Virbac, Milperra, NSW, Australia) and 0.04 mg/kg medetomidine (Bova, Caringbah, NSW, Australia) intramuscularly using a dart delivery system (a 1.5 mL syringe with the deployed syringe set at a two bar projectile pressure) (Dan-Inject Rifle, Austin, TX, USA). The orangutan was intubated using an 8.0 mm cuffed endotracheal tube and maintained on isoflurane gas (1.5-2.0% at 2000 mL/min O_2). The hemodynamics were preserved with an intravenous fluid therapy (Hartmann's Solution, 10.5 mL/kg/hour). The clinical parameters were monitored; these included the heart rate, respiratory rate and mean blood pressure, which were maintained at 70-80 beats/min, 30 breaths/min and 50-60 mm Hg, respectively, throughout the procedure. The body temperature was maintained at approximately 37.0°C by placing the orangutan on a heated

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blanket (Bair Hugger3M, North Ryde, NSW, Australia). Prior to the endoscopy, the orangutan was administered half the amount of a reversal agent to counter the medetomidine component of the induction regime and to improve the cardiovascular function (0.1 mg/kg atipamezole intramuscularly; Ilium Atipamezole® Troy Laboratories, Glendenning, NSW, Australia). Following the completion of the procedure, the orangutan was administered the remaining reversal agent (atipamezole, 0.1 mg/kg intravenously). This anesthesia protocol was used for all the procedures described in this report.

The orangutan recovered uneventfully within her enclosure and within two hours post-surgery. The orangutan was then provided with 5.2 mg/kg of ibuprofen (Nurofen®, Reckitt Benckiser Pty Limited, Sydney, NSW, Australia) per os twice daily for three days for post-surgical analgesia and began a fluconazole 6 mg/kg per os twice daily (Sandoz, Macquarie Park, NSW, Australia) treatment for a suspected fungal infection for four weeks post-endoscopy.

Fungal identification and medical treatment

Endoscopic surgical procedure was used to excise the mass and debride the underlying infected tissue under anesthesia. This procedure involved the introduction of a 2.7 mm rigid telescope (Storz Endoscopy, Sydney, NSW, Australia) into the dorsal aspect of the right nasal cavity. This was the location of the fungal mass that extended from the right dorsal turbinate into the rostral aspect of the nasal cavity, the fungal mass was removed (Straightshot M5 Microdebrider, Medtronic, North Ryde, NSW, Australia). There were no complications or unexpected morbidities associated with the diagnostic procedure.

To determine the causative fungal agent of the rhinosinusitis, the collected fungal mass and debrided underlying mucosa were co-cultured on brain-heart infusion agar with chloramphenicol and Sabouraud dextrose agar with chloramphenicol at 35.0°C and 30.0°C for 3 days, respectively. The abundant fungal growth (data not shown) and the presence of conidia with transverse septa and prominent terminal tapered ends on the histopathology were indicative of the genus *Curvularia*. In addition, a PCR analysis of the targeted internal transcribed spacer 1 and 2 regions of the fungal ribosomal gene cluster (PCR primer ITS1; TCCGTAGGTGAACCTGCGG; IST2 GCTGCGTTCTTCATCGATGC) in reference with the ISHAM-ITS database and in concert with a secondary characterization of the fungus using MALDI-TOF-confirmed the fungus was *Curvularia*. The identification of *Curvularia* and the histopathological tissue findings were also well-aligned with the observations of *Curvularia* infections in humans and other mammalian species, further supporting the diagnosis of *Curvularia* as the causative agent of rhinosinusitis in the Sumatran orangutan.

A final diagnostic endoscopic procedure 13 weeks after the fungal mass excision was completed to ensure that there was no residual mass or inflamed or necrotic tissue within the right nasal cavity and right maxillary sinus. The endoscopy showed complete resolution of the infection. Following the diagnostic endoscopy, the fungal treatment was adjusted from fluconazole to itraconazole. Many dematiaceous fungal species have developed a significant resistance to fluconazole treatments whilst remaining relatively susceptible to an itraconazole therapy.

Discussion

In general, the anatomical structure of the URT of NHPs includes the nasal and paranasal sinus cavities, nasopharynx, larynx, air sacs (in several NHP species), trachea and large bronchi. Infections within these structures can occur at different rates and can be infected by pathogens or, in a few instances, opportunistic organisms. As an example, airsaculitis is common in many NHPs and is associated with etiologies that include viruses and bacteria, with severe incidents of the disease being associated with infections of mixed populations of microorganisms. Similar to airsacculitis, infections with multiple microorganisms can occur in the nasal cavities and paranasal sinuses of orangutans. It has been suggested that air sac infections may result from exudates draining the nasal and paranasal sinus cavities and subsequently pooling in the air sacs. This was not determined as a source of infection for the orangutan in our case.

Naturally occurring (non-experimental) incidences of nasal and paranasal sinus fungal infections in NHPs are not well-documented. There are reported incidences of pulmonary disease caused by various fungi, but concurrent nasal or paranasal sinus infections are either not determined or investigated in clinical studies. This is surprising, as nasal or paranasal sinus infections should readily act as a source for lung infections. Perhaps this observation reflects the ability of the fungi to colonize the respiratory mucosa or possibly our narrow understanding of the process; as there appears to be limited knowledge of fungal ecology and diversity in various NHP species. In addition, this observation contrasts with the conspicuously higher incidence of primary bacterial infections within the nasal cavities and paranasal sinuses, further suggesting a limited understanding of the colonization and pathogenesis of fungi in the upper respiratory tract. Accordingly, the identification of rhinosinusitis in endangered species-e.g., the orang-utan and its association as an opportunistic emerging fungal pathogen is of particular interest. As such and to the best knowledge of the authors, this is the first reported case of primary fungal rhinosinusitis in a Sumatran orangutan caused by *Curvularia sp*.

Conclusion

The cause of a right-sided epistaxis in a female Sumatran orangutan was investigated. Various diagnostic procedures, including an endoscopic biopsy, the blood lymphocyte profile, the serum viral antibody titers, the histopathology and CT imagery were used to determine the cause of the epistaxis. It was identified, to the best knowledge of the authors, that this was the first reported incidence of a unilateral nasal and paranasal sinus infection in an orangutan caused by the dematiaceous fungus *Curvularia*. Endoscopic sinus surgery was used to successfully excise and debride the infected tissues and, with an adjunctive antifungal therapy, the procedure was curative and there was no recurrence of infection or disease.

Acknowledgement

None.

Conflict of Interest

None.

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