



Case Report

Anatomopathological findings and identification of *Cryptococcus gattii* in a captive African pygmy hedgehog (*Atelerix albiventris*)

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Abstract

The African pygmy hedgehog (*Atelerix albiventris*) is becoming increasingly common in zoological collection and as pets, increasing the risk of disease transmission. Here, we describe a case of cryptococcosis caused by *Cryptococcus gattii* in a captive African pygmy hedgehog and the other anatomopathological findings. The macroscopic analysis of the lung found white-yellowish masses of gelatinous consistency. The microscopic analysis of the lung revealed severe pulmonary involvement resulting from granulomatous pneumonia caused by *C. gattii* yeasts, identified through polymerase chain reaction and sequencing. Other histopathological findings included hepatic steatosis, biliary hyperplasia, and renal lesions with deposition of hyaline cylinders in the lumen of tubular epithelial cells, glomerulopathy, and tubular necrosis. Our findings demonstrate the importance of anatomopathological studies in diagnosing relevant diseases in the context of one health. We emphasize that adequate environmental management is essential to avoid the emergence of certain diseases in captivity.

Keywords: pathology, cryptococcosis, captive African pygmy hedgehogs

Introduction

Cryptococcosis is an opportunistic zoonosis caused by encapsulated yeasts of the fungal genus *Cryptococcus* (5, 17, 30). This fungal taxon contains at least 39 species, but *Cryptococcus gattii* and *C. neoformans* are the ones that most infect humans and other animals (5, 17, 31). *Cryptococcus neoformans* is an opportunistic pathogen that infects immunocompromised hosts (2, 6, 22). It is the most prevalent *Cryptococcus* species, with global distribution and occurrence associated with pigeon guano and soil rich in organic matter (5, 18, 30). *Cryptococcus gattii* is a primary pathogen that infects immunocompetent hosts (21, 22). This pathogen is more narrowly distributed and commonly associated with

trees, first discovered in *Eucalyptus camaldulensis* (9) and later found in other *Eucalyptus* species (25). However, *C. gattii* has already been identified in more tree species, such as *Guettarda acreana* in the Brazilian Amazon, which suggests that this fungus also inhabits tropical forests (11).

In humans and other animals, *Cryptococcus* infection occurs by inhaling basidiospores or yeasts present in the environment or dried bird (mainly the pigeon *Columba livia*) excreta (4, 10, 30). Inhaled infectious particles can colonize the upper and lower respiratory tract and spread through the bloodstream to other organs and the central nervous system (4, 30). Infection prevails mainly in the upper respiratory tract because the encapsulated yeasts are larger than the terminal

airways (4, 33). However, if the capsule is lost or reduced, cells rapidly lose viability and are no longer infectious (4, 33).

The African pygmy hedgehog (*Atelerix albiventris*) is a member of the family Erinaceidae and a small nocturnal mammal native to West, Central, and East Africa, where it occupies a diversity of habitats such as grasslands, shrublands, savannas, and suburban gardens (14). This species has gained increasing interest as an exotic pet (13). Several retrospective studies have addressed disease incidence in hedgehogs (12, 16, 23). One of these studies found that the gastrointestinal and integumentary systems are the most affected in captive hedgehogs (12). Infectious diseases such as tuberculosis have also been detected, which stresses the importance of hedgehogs for public health (29). In a European hedgehog (*Erinaceus europaeus*), infection with *C. gattii* (identified by polymerase chain reaction) caused granulomatous meningoencephalitis, granulomatous ventriculitis and choroiditis, hydrocephalus, and numerous intrahistiocytic and extracellular yeasts (32). However, given the zoonotic potential of these increasingly popular animals as exotic pets, further diagnostic studies of infectious diseases in hedgehogs are still needed.

Here, we describe the anatomopathological findings of an African pygmy hedgehog (*Atelerix albiventris*) that died from respiratory failure caused by a fungal infection with *C. gattii*.

Case description

On 24 February 2022, an adult female African pygmy hedgehog (*Atelerix albiventris*) was voluntarily sent to the Associação Mata Ciliar (AMC), municipality of Jundiá, state of São Paulo. At AMC, she was fed cat food daily and mealworms (*Tenebrio molitor* and *Zophobas morio*) twice weekly. The hedgehog was healthy until 13 July 2022, when a physical examination indicated incoordination, dyspnea, bradycardia, and thoracic and pelvic limb paresis. The hedgehog died the next day.

At necropsy, the organs were evaluated macroscopically. Tissue samples from lung, kidney, liver, brain, cerebellum, adrenal, spleen, and gastrointestinal tract were collected and fixed in a 10% phosphate-buffered formalin solution (pH 7.4), processed by the standard paraffin method, cut at 5 µm, and stained with hematoxylin and eosin and Periodic Acid-Schiff (PAS).

External examination indicated a normal body condition without substantial alterations. Internal examination revealed markedly distended and turgid lung lobes tightly adhered to the diaphragm (Figure 1A-B). These lobes had white-yellowish masses of gelatinous consistency (Figure 1A-B). The liver showed a moderately accentuated lobular pattern and slightly distended edges; on dissection, the liver had a friable consistency (Figure 1C). The spleen showed mild splenomegaly. The kidney had multifocal petechiae in the capsule and striations in the cortical region. The other organs showed no macroscopic alterations.

Histopathological evaluation of the lungs revealed spherical and ovoid structures with a basophilic cell wall and a thick clear halo, indicated by the gelatinous capsule unstained with hematoxylin and eosin (Figure 2A). These structures were morphologically compatible with *Cryptococcus* sp. fungal yeasts (Figure 2A). The thick yeast capsule was composed of mucopolysaccharides, as evidenced by the positive reaction to PAS (Figure 2B). Around these yeasts, we observed a marked inflammatory infiltrate of lymphocytes, neutrophils, plasma cells, and macrophages (Figure 2C), thus characterizing granulomatous pneumonia. Moreover, we identified extensive areas of multifocal necrosis, alveolar edema, and alveolar congestion.

Histopathological evaluation of the liver revealed a marked ductular reaction, lymphoplasmacytic cholangitis, and fibrosis (Figure 3A-B). The liver also showed micro and macro spherical droplets and well-defined edges displacing the hepatocyte nucleus to the periphery, with multifocal distribution, compatible with hepatic steatosis (Figure 3C). The kidney evaluation revealed vacuoles similar to those found in the liver, as well as tubular proteinosis, tubular necrosis (Figure 4A), and thickening of Bowman's capsule and the basal membrane of the glomerular capillaries. The positive reaction to PAS was suggestive of membranous glomerulonephritis (Figure 4B). The lumen of the small intestine had coccus-like bacterial colonies associated with a polymorphonuclear inflammatory infiltrate composed primarily of neutrophils, thus characterizing acute neutrophilic enteritis. The brain and cerebellum showed edematous interstitium, but we found no structures compatible with the fungal yeasts described in the lung. The other organs showed no microscopic alterations.

We performed a polymerase chain reaction (PCR) to identify the fungal species. DNA from fresh frozen lung tissue fragments was extracted with a silica-based column nucleic acid purification technology following the manufacturer's instructions (Bio Gene Extração de DNA/RNA Viral, Bioclin, Belo Horizonte, Brazil). PCR was performed using the primers ITS3 (5'-GCATCGATGAAGAACGCA GC-3') and ITS4 (5'-TCCTCCGCTTATTGATATGC-3') with GoTaq® Green Master Mix (Promega, WI, USA) and 5 µL of the DNA in a 25 µL reaction volume. Thermal cycler conditions consisted of 5 min at 95 °C; 40 cycles at 95 °C for 30 sec, 55 °C for 60 sec, and 72 °C for 30 sec, and a final extension step at 72 °C for 10 min. Purified genomic DNA from *Aspergillus* spp. external proficiency test (Controllab, Rio de Janeiro, RJ, Brazil) and nuclease-free water were applied as positive and negative controls, respectively. Amplicons were visualized on a 2% agarose gel using a Gel Doc EZ Gel Documentation System (Bio-Rad, Hercules, CA, USA). Sequencing was performed with the ABI Big Dye Terminator cycle sequencing kit on an automated sequencer (ABI Prism 3500 Genetic Analyzer; Applied Biosystems, Foster City, CA, USA). The chromatograms were manually edited with BioEdit v.7.2. A-427 pb assembled contig was subjected to a similarity search in the GenBank/EMBL/DDBJ database using the

Blast 2.13.0 software (<https://blast.ncbi.nlm.nih.gov/Blast.cgi>) and MycoBank Database (https://www.mycobank.org/page/Pairwise_alignment).

The sequence obtained (Table 1) showed 95.33% homology with a region of the internal transcript sequence of the *Cryptococcus gattii* strain (GenBank acc # KY107034.1) with 100% coverage. Through Mycobank database analysis, the similarity was 95.08 % with *Cryptococcus deuterogattii* strains (accession number MIRRI0039957 and CBS 11257). Low similarity scores were obtained with *Cryptococcus neoformans* var. *grubii* (GenBank acc # CP048088.1, CP048073.1, MH203397.1 with 95.08% homology and MycoBank acc # CNRMA13.698 with 94.61% homology).

Discussion

Cryptococcus gattii is an emerging fungus with an expanding area of occurrence (5). This pathogen reproduces

asexually by budding yeasts and sexually by producing spores (2). Inhalation of yeasts and spores can cause infections in various domestic and wild animals, including humans (5). The hedgehog of the present report had a pulmonary infection with *C. gattii*. However, the hedgehog probably had no compromised immune response because *C. gattii* is a primary pathogen infecting immunocompetent hosts (18).

The hedgehog died from respiratory failure resulting from a fungal infection with *C. gattii*. This study is the first report of fungal infection with *C. gattii* in the African pygmy hedgehog. In the European hedgehog, *Erinaceus europaeus*, infection with *Cryptococcus neoformans* var. *gattii* did not compromise the lungs but they caused granulomatous meningoencephalitis (32), as described in dogs — which develop a marked inflammatory response, mainly mixed and granulomatous — and unlike to that described in cats — which usually develop a mild response, mainly neutrophilic (31).

Histopathological findings similar to those found in the hedgehog lung have also been described in other animal

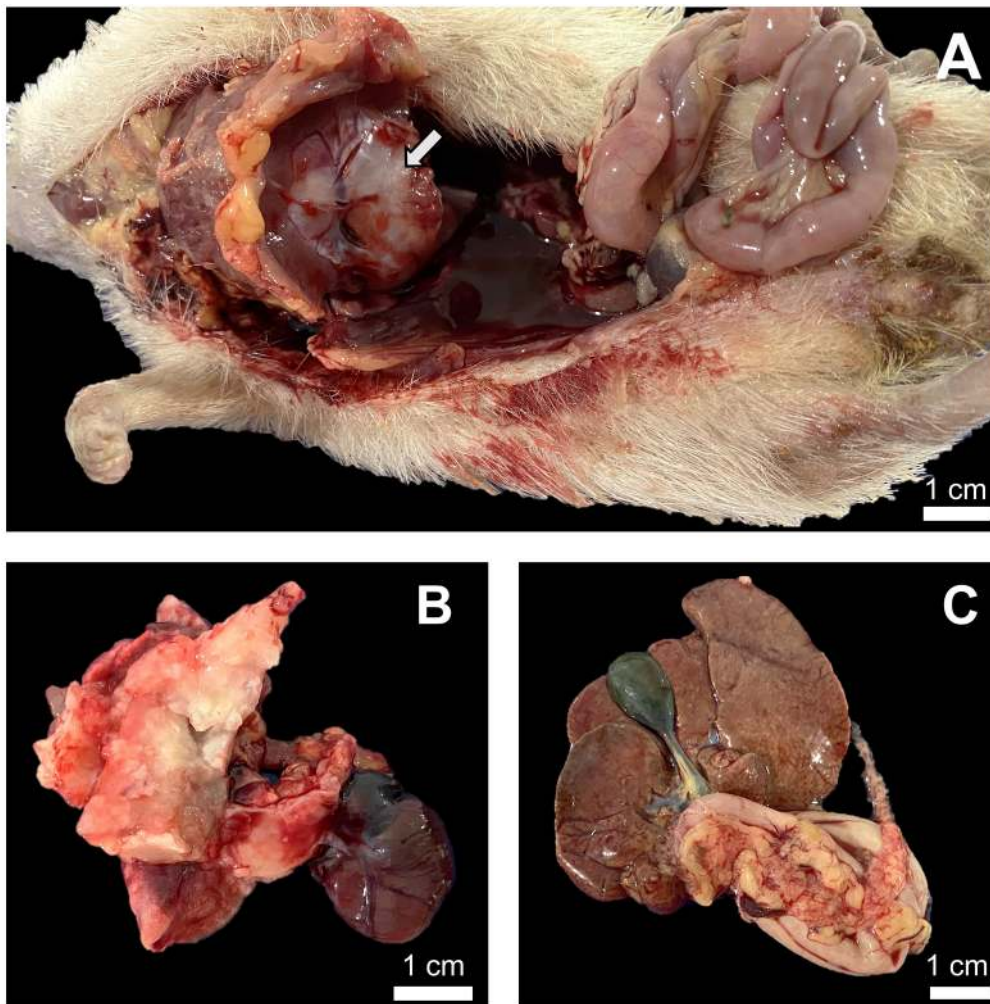


Figure 1. Postmortem examination of an adult female African pygmy hedgehog (*Atelerix albiventris*). A- Lungs showing a gelatinous, yellowish-white material adhered to the diaphragm (white arrow). B- Detail of the gelatinous, yellowish-white material in the lung. C- Liver with discrete hepatomegaly and accentuation of the normal lobular pattern.

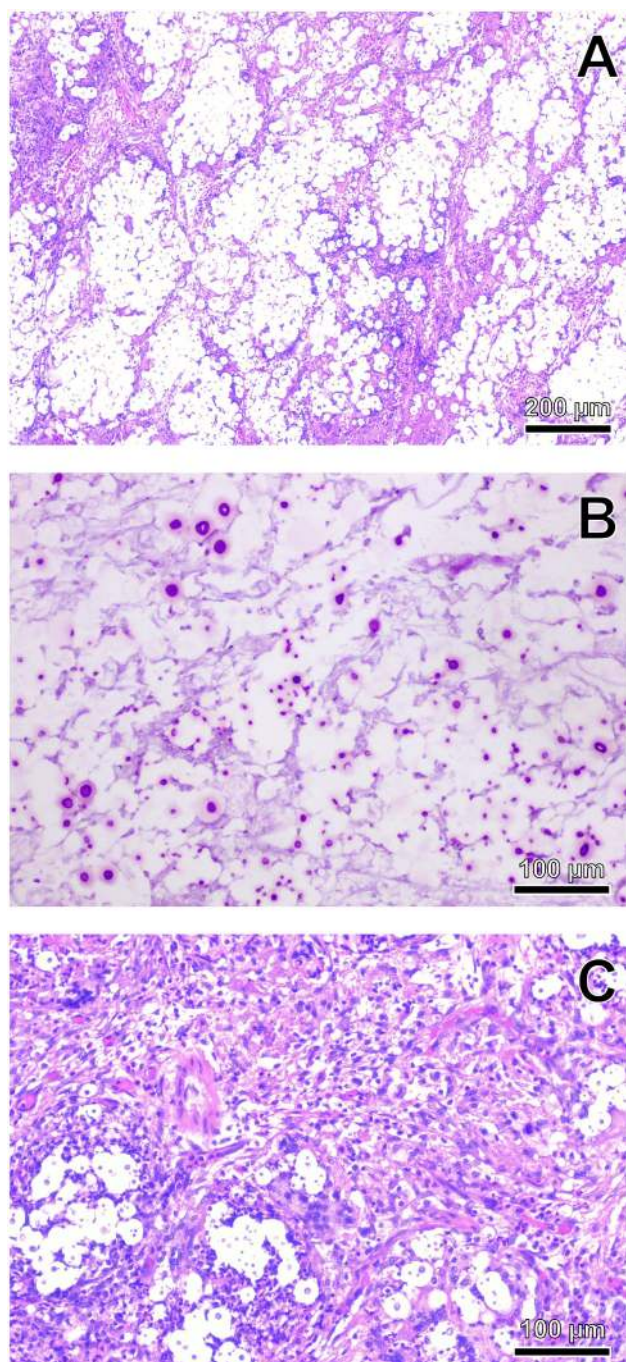


Figure 2. Histopathological evaluation of the lung of an adult female African pygmy hedgehog (*Atelerix albiventris*). A- Spherical and ovoid structures with a basophilic cell wall and a thick clear halo, morphologically compatible with *Cryptococcus* sp., as indicated by the gelatinous capsule unstained. HE, bar = 200 µm. B- Structures morphologically compatible with fungal yeasts containing a thick capsule composed of mucopolysaccharides evidenced by the positive reaction to Periodic Acid-Schiff (PAS). Bar = 100 µm. C- Diffuse granulomatous pneumonia containing inflammatory infiltrate composed of lymphocytes, neutrophils, and macrophages around fungal yeasts. HE, bar = 100 µm.

species infected with *C. gattii*. For example, granulomatous pneumonia and extracellular and intrahistiocytic fungal yeasts have also been observed in the rhesus macaque *Macaca mulatta* (15). However, in this primate species, yeasts were also found within the heart, pancreas, kidneys, stomach, and colon, often associated with inflammatory reactions (15). In a citron-crested cockatoo (*Cacatua sulphurea citrinocristata*), disseminated cryptococcosis affected several organs, such as the beak, lungs, spleen, and brain (19).

Cryptococcus gattii is mainly associated with tropical and subtropical regions of Australia, Africa, South America, and southern Asia. However, its occurrence on the Pacific coast of North America has been reported since the 2000s (7, 20). For example, *C. gattii* has been isolated from the nasal swabs of eastern gray squirrels (*Sciurus carolinensis*) from Canada (8). In nature, *C. gattii* occurs mainly in eucalyptus trees (27, 29), but it has also been identified in fecal samples of Psittaciformes (1). It is unclear how the hedgehog of the present report was exposed to *C. gattii*. However, the hedgehog was kept in a metal cage with wood shavings (possibly eucalyptus) as a substrate in an environment shared with blue-fronted Amazon parrots (*Amazona aestiva*).

In addition to cryptococcosis, the hedgehog showed other pathologies previously described in this species, such as hepatic steatosis (16, 23, 26, 28). This commonly reported disease in postmortem examinations of hedgehogs may be related to a change in lipid metabolism caused by reduced food consumption in the days preceding the hedgehog's death. Another important pathological finding was biliary hyperplasia, which has been recently reported together with steatosis in African pigmy hedgehogs (28). We also found fat vacuoles in the tubular cells of the hedgehog kidneys. In dogs and cats, kidney fat is believed not to substantially alter their function, as these organs regularly store fat in the proximal tubules (3). Other alterations, such as tubular necrosis and glomerulopathy, have already been described in studies characterizing kidney lesions in hedgehogs. In a retrospective study of postmortem examinations, 50% of the African pigmy hedgehogs evaluated showed these alterations (26).

Pathogenic *Cryptococcus* species cause disease in about one million individuals annually (with over 620,000 attributable deaths), and cryptococcal meningitis is one of the most important HIV-related opportunistic infections, particularly in the developing world (24). Cryptococcosis is, therefore, a zoonosis of worldwide importance, and diagnostic studies of this disease in different species worldwide are relevant to understand the epidemiological context of this disease better.

In summary, it is essential to clarify that this hedgehog could not transmit this disease directly to humans or other animal species. However, its death may indicate possible sources of infection of *C. gattii* yeasts in the environment in which it lived. We could not determine the source of the *C. gattii* yeasts. However, we highlight

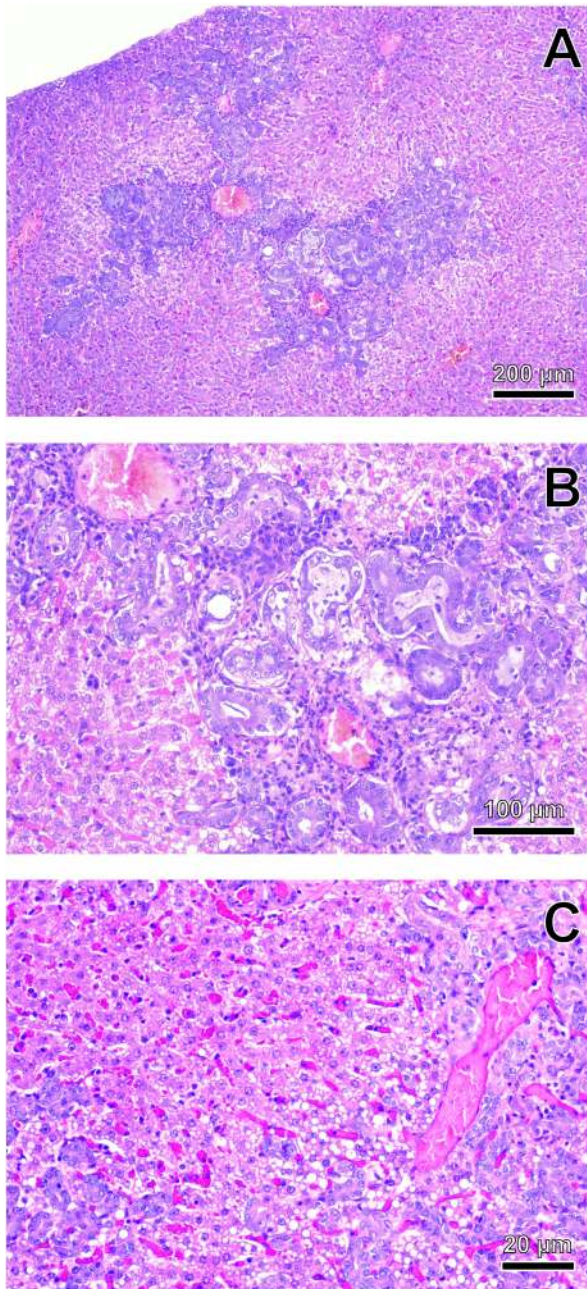


Figure 3. Histopathological evaluation of the liver of an adult female African pygmy hedgehog (*Atelerix albiventris*). A- Bile duct hyperplasia, congested vessels, and macro- and microvesicular steatosis. HE, bar = 200 µm. B- Bile duct hyperplasia with chronic cholangitis. Note the hyperplastic bile ducts lined by cuboidal to polygonal epithelial cells. HE, bar = 100 µm. C- Diffuse macro- and microvesicular steatosis. HE, bar = 20 µm.

the importance of evaluating the quality and source of the substrate offered to these animals, as these materials can be the source of certain infections. Moreover, birds and other mammal species should not share the same room in captivity, as this may facilitate the spread of pathogens. Diagnosing cryptococcosis and other incidental pathological processes found in the African pygmy hedgehog raises opportunities for further studies in this species. The fact that this species is increasingly becoming pets favors the transmission of diseases, thus making specific medical knowledge and care essential.

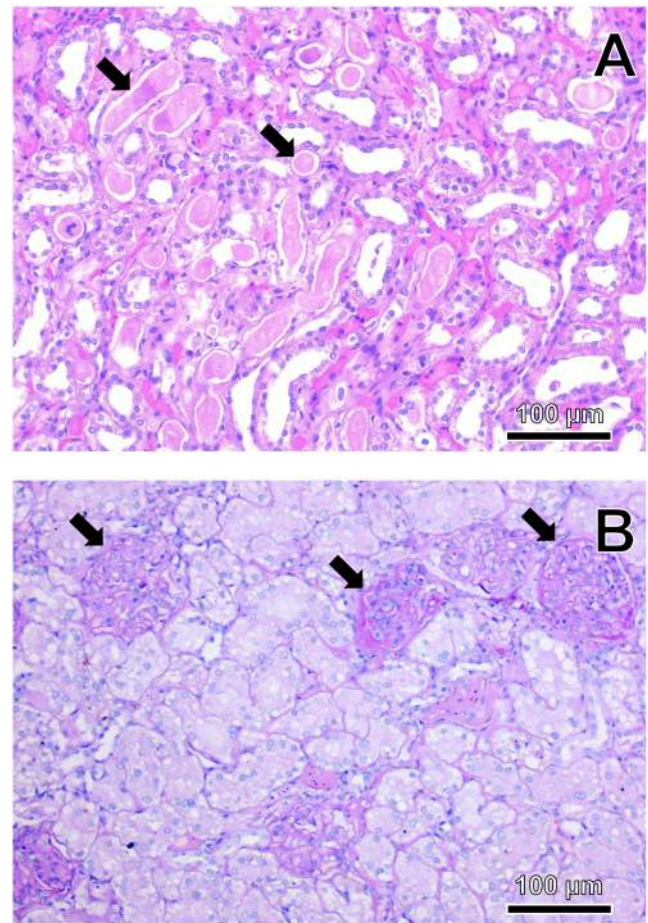


Figure 4. Histopathological evaluation of the kidney of an adult female African pygmy hedgehog (*Atelerix albiventris*). A- Tubular proteinosis (black arrows). HE, bar = 100 µm. B- Thickening of Bowman's capsule and basal membrane of glomerular capillaries characterizing membranous glomerulonephritis (black arrows). Periodic Acid-Schiff (PAS), bar = 100 µm.

Table 1. DNA sequence obtained from fresh frozen lung tissue fragments.

DNA sequence
GCATATCAATAAGCGGAGGAAAAGAACTAACAAAGGATTCCTTAGTAACACCGGGAAGACACCGGGAAGAGCTCAAATTTGAAATC-TGGCGTCTCCGGGCGTACGAGTTGTATCTACAGAAACGTTTTCCGTGCTGGTCCGTGTCTAAGTCCCTTGAATAGGGTATCAAA-GAGGGTGACAATCCCGTACTTGACACGATACCCAGTGCTCTGTGATACGTGTTGTACGAGTCGCGTACTTGGGAGTGTAGCGCAA

Conflict of Interest

The authors declare no competing interests.

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