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Gingival histoplasmosis: An atypical presentation of African Histoplasmosis in three baboons (*Papio spp*).

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Abstract

Gingival lesions as the sole manifestation of African histoplasmosis (*Histoplasma capsulatum* var. *duboisii*) have never been reported in baboons. Grossly, lesions can be indistinguishable from bacterial ulcerative gingivitis or gingival hyperplasia. Clinical outcomes of primary gingival histoplasmosis in baboons are unknown, and, may complicate colony management decisions.

Keywords

Non-human primate; Baboon; Mycosis; Oral; *Histoplasma capsulatum* var. *duboisii*

Introduction

African histoplasmosis is an opportunistic fungal disease in humans caused by *Histoplasma capsulatum* var. *duboisii* (HCD) [1–5]. The epidemiology and modes of transmission are poorly understood [3, 6, 7]. Urine and serum antigen detection tests cannot distinguish *Histoplasma* varieties *duboisii* from *capsulatum* (HCC) [3, 5, 8]. Definitive diagnosis is achieved via culture and histopathology [3, 6]; HCD yeast in infected tissues are larger with thicker walls than their HCC counterpart [2–4, 9].

Localized or solitary HCD result in focal lesions of the skin, bone or lacrimal gland [10]. Disseminated disease may involve multiple sites including: skin, reticuloendothelial system, lymph nodes, abdominal organs, oral cavity and bone [1, 4, 6, 11–13]. Disseminated disease has a poor clinical and treatment outcome [1, 3–5, 10, 14]. There are sporadic reports of HCD within the oral cavity involving the tonsil, buccal mucosa, tongue, gingiva, maxillary and mandibular bones [1, 12–16].

African histoplasmosis almost exclusively presents as granulomatous dermatitis in baboons [9, 17–20]. Typical baboon HCD lesions consist of umbilicated cutaneous ulcers localized to

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extremities and head with occasional regional lymph node and bone involvement [17–21]. To the best of our knowledge, this is the first report of primary gingival African histoplasmosis in baboons.

Case Report

Baboons were housed in two open-top 6-acre metal and concrete corrals with dirt floors or gang cages with concrete floors. HCD is endemic within our population of captive baboons regardless of where the animals are maintained or housed [19]. All procedures were approved by the Texas Biomedical Research Institute (TBRI) Institutional Animal Care and Use Committee. TBRI is an AAALAC-accredited institution.

Relevant case information is summarized in Table 1. Baboons 1 was a naïve juvenile in a production colony, the lesions progressed over six months, and no radiographic changes were seen. Oral lesions were characterized by gingival reddening and thickening (Figure 1 A and B). Baboon 2 was assigned to a reproductive study, and the gingival lesions were an incidental finding at necropsy. Baboon 3 was previously enrolled in a periodontal disease study as an unaffected control and diagnosis was made three years prior to euthanasia. None of the animals were related; all HCD lesions were limited to the oral cavity and diagnoses were confirmed by histopathology.

Histology was performed on necropsy (Baboons 1 and 2) and biopsy (Baboons 1 and 3) samples. Tissues were fixed in 10% neutral buffered formalin, processed conventionally, embedded in paraffin, cut at 5 µm, and stained with hematoxylin and eosin, Gomori's Methanamine Silver (GMS), Ziehl-Neelsen stain (acid fast), and using Periodic Acid-Schiff procedure (PAS). All necropsy and histopathology procedures were performed by a board certified veterinary pathologist.

Histopathology identified a predominant population of macrophages and multinucleated giant cells with myriad intracytoplasmic and extracellular round to oval fungal yeast that expanded the submucosa and elevated the overlying hyperplastic, segmentally eroded, and occasionally ulcerated mucosal epithelium (Figure 2A, Figure 2B, Figure 2C). Yeast ranged from 7–10 µm with a 2µm thick, clear, negative staining capsule, light staining amphophilic central area (Figure 2B, Figure 2C, Figure 2D), and narrow base budding (Figure 2F). The yeast wall stained pink with PAS (Figure 2F) and black with GMS (Figure 2E). Internal structures of the yeast were acid fast negative (results not shown). Localized microscopic bone involvement was confirmed in Baboon 1(Figure 2A); subjacent bone was not present in samples from Baboons 2 and 3. Maxillary bone radiographs (Baboon 1) were inconclusive, possibly below the limits of radiographic detection. Radiographs were not obtained for Baboons 2 and 3.

Discussion

We present the first report of primary gingival African histoplasmosis in three baboons. Characteristic lesions involve aggregates of macrophages and multinucleate giant cells containing myriad GMS and PAS positive intracellular yeasts measuring 7–10µm in diameter with thick walls and narrow-based budding with similar morphology as described

in human case reports [1, 3, 6, 18, 21–23]. Based on the lack of other tissue involvement at gross necropsy in all three animals, and by histopathology in two of the three animals, these lesions appear to be localized to the gingiva alone.

While diagnosis of HCD is relatively straightforward, the implications for colony management are complicated by basic epidemiological questions concerning the long incubation period and unclear mode of transmission, as the portal of entry of has not been definitively established. Respiratory transmission from soil contaminated with HCD is generally accepted as most probable [2, 3, 18], however the absence of pulmonary involvement in the majority of HCD cases challenges this idea [12, 24]. It has been suggested that grooming behaviors of baboons, including licking, picking, and ingesting material from lesions, could explain the transmission of this disease amongst members of the colony [18, 21]. Primary inoculation of the skin has been documented as a cause of cutaneous histoplasmosis in humans [4, 25], implying that the disease can be transmitted via direct contact[18]. The dam of Baboon 1 had been diagnosed with African histoplasmosis prior to the animal's birth, suggesting the possibility of direct transmission; however, we cannot exclude other sources of infection. Protocol enrollment of Baboon 3, as a control animal, only involved targeted oral examinations potentially resulting in enhanced sensitivity for detection of oral lesions.

Oral lesions as in our baboons are well-documented in human cases of disseminated HCD [1, 12, 15, 16, 23, 26]. However, oral lesions as the sole manifestation of HCD in humans are uncommon, and their status as primary localized lesions is questionable [13, 14]. This association of oral lesions with systemic disease in HCD complicates management decisions in baboons with apparently localized gingival lesions since diagnosis of HCD dermatitis is a common reason for euthanasia [19]. If oral lesions are indeed an early manifestation of systemic disease, then the long-term prognosis for the animal would be poor, however, there is no evidence supporting systemic disease in the baboons presented in this case report. Chemotherapeutical treatment in cases of disseminated disease has been historically unsuccessful in baboons [9, 18, 27]. Truly localized lesions of HCD have been successfully treated with surgical excision [9, 18]. While spontaneous regression of isolated oral histoplasmosis lesions has been recorded in human medicine, it is exceptionally rare [1, 13, 23].

We present the first report of gingival lesions as the primary manifestation of HCD in baboons and represents an additional site to monitor in this species. The gross appearance of gingival lesions caused by HCD in baboons is not unique; differentials include gingivitis, gingival hyperplasia[28], periodontal disease [29], squamous cell carcinoma [30] and other mycotic infections [31]. HCD should be considered as a differential when evaluating gingival lesions in baboons. A definitive diagnosis of HCD complicates colony management decisions, since the natural history of this disease remains unclear.

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Figure 1.

Gross images of oral cavity lesions of Baboon 1 at different time points shows progression of disease.

A) Image taken at biopsy. Note multifocal to coalescing raised nodules with areas of ulceration on the anterior maxillary gingiva.

B) Image taken at necropsy 1 month after biopsy. Note multifocal to coalescing raised pale tan nodules on anterior maxillary gingiva.

Figure 2.

Histopathology of oral lesions of Baboon 1 obtained at the time of necropsy (Images A-C). Histopathology of oral lesions of Baboon 1 obtained at the time of biopsy (Images D-F).

A) Coronal section of maxilla including gingiva (G), submucosa (SM), maxillary alveolar bone (AB) and tooth dentin (D). Area of expanded submucosa is delineated by horizontal black line. H&E. Bar = 200µm.

B) Higher magnification of Figure A demonstrating bone remolding adjacent to a focus granulomatous inflammation. Yeast are visible within macrophages. H&E. Bar = 20µm.

- C) Higher magnification of Figure A demonstrating gingival hyperplasia subtended by dense granulomatous inflammation. Yeast are visible within macrophages. H&E. Bar = 20µm.
- D) Multinucleated giant cell containing intracytoplasmic HCD yeast. H&E. Bar = 20µm.
- E) HCD yeast stain black with GMS stain. GMS. Bar = 20µm.
- F) HCD yeast capsules stain bright pink with PAS stain. Yeast narrow based budding indicated by short arrow. PAS stain. Bar = 20µm.

Table 1.

Baboon demographic, biopsy and necropsy information.

Animal	Age	Sex	Gross findings	Biopsy/Necropsy	Protocol	Comments
Baboon 1	1y 9m	F	Gingival thickening and reddening	Biopsy Y/ Necropsy Y	Naïve	Euthanized due to HCD diagnosis
Baboon 2	6y 11m	F	Gingival thickening and reddening	Biopsy N/ Necropsy Y	Reproductive protocol	Gingival lesions first noted at necropsy
Baboon 3	10y 8m	F	Gingival hyperplasia with increased tissue fragility	Biopsy Y/ Necropsy Y*	Control animal for periodontal disease study	Euthanized 3y after HCD diagnosis. No gross lesions were identified at necropsy.

* Gross necropsy only

y: years; m: months; F: Female; Y: Yes; N: No