

Histoplasmosis in a cat

A 1-year-old, castrated male, Domestic Shorthair cat presented with nasal congestion, weight loss, and clear oculonasal discharge. The cat had been found by the owner 7 months prior and the cat's prior medical history was unknown. On physical exam, multiple 3-4 mm in diameter, raised, thickened, alopecic areas with multiple crusts and ulcerations were noted along the bridge of the nose and the right eyelid. He was given a Convenia injection, but presented 2 weeks later with many more lesions, which had progressed to cover the proximal right ear margin and the entire nasal planum, imparting a "Roman nose" appearance. The cat had stertorous breathing, but thoracic radiographs and CBC/chemistry were normal. The patient resided in Texas and had no known travel history outside the state.

Figure 1:



Figure 2: H&E, 20x

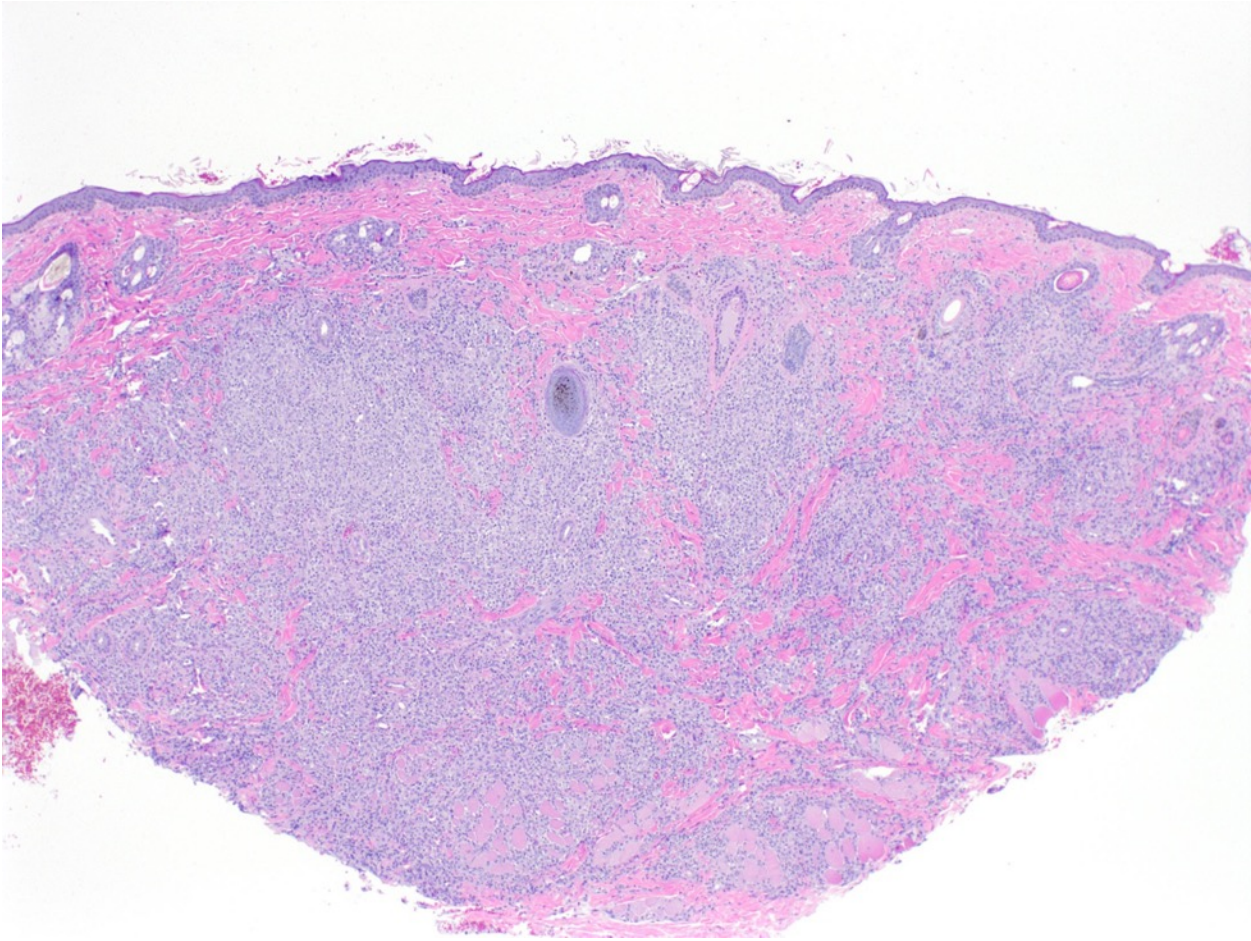


Figure 3: H&E, 100x

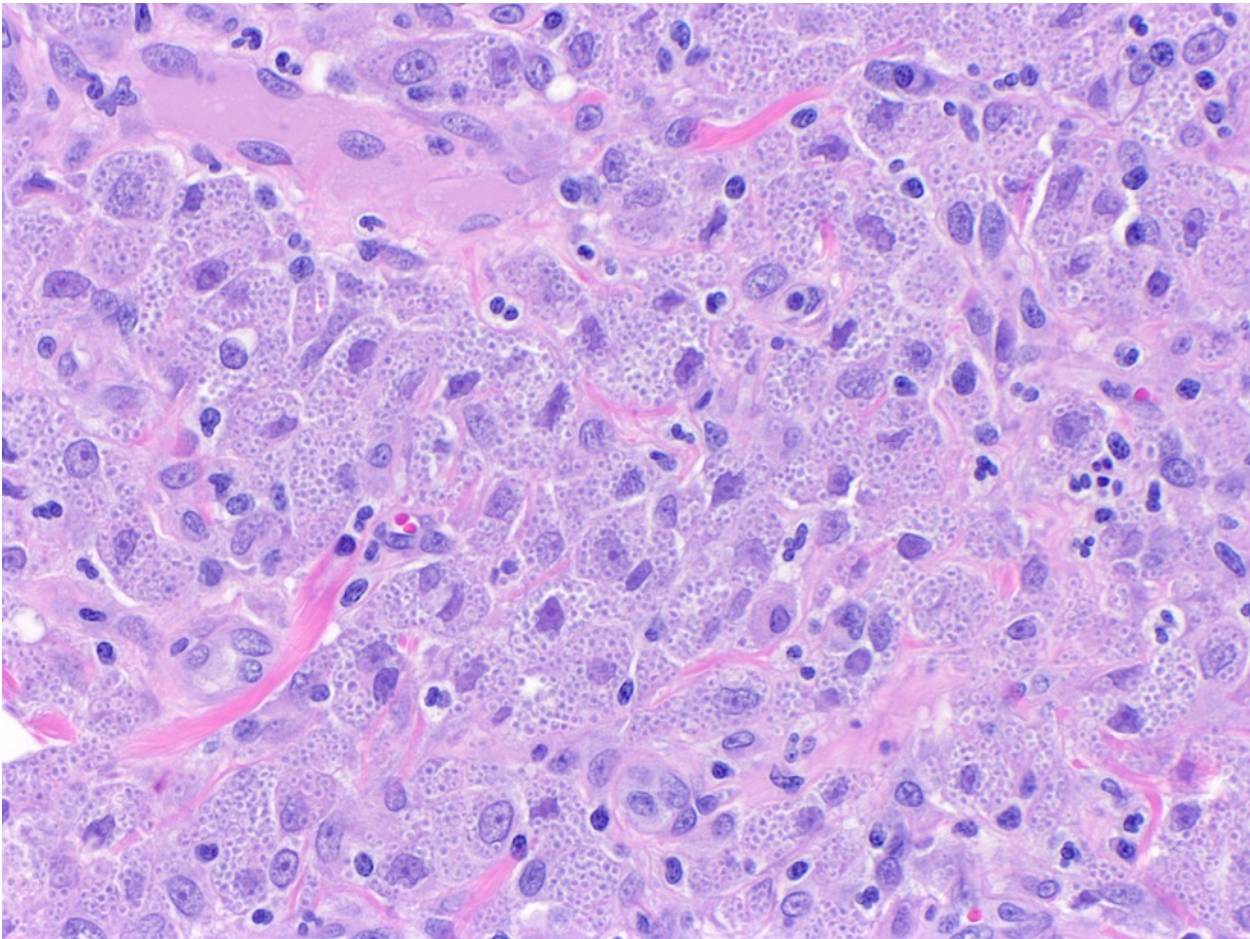


Figure 4: H&E, 200x

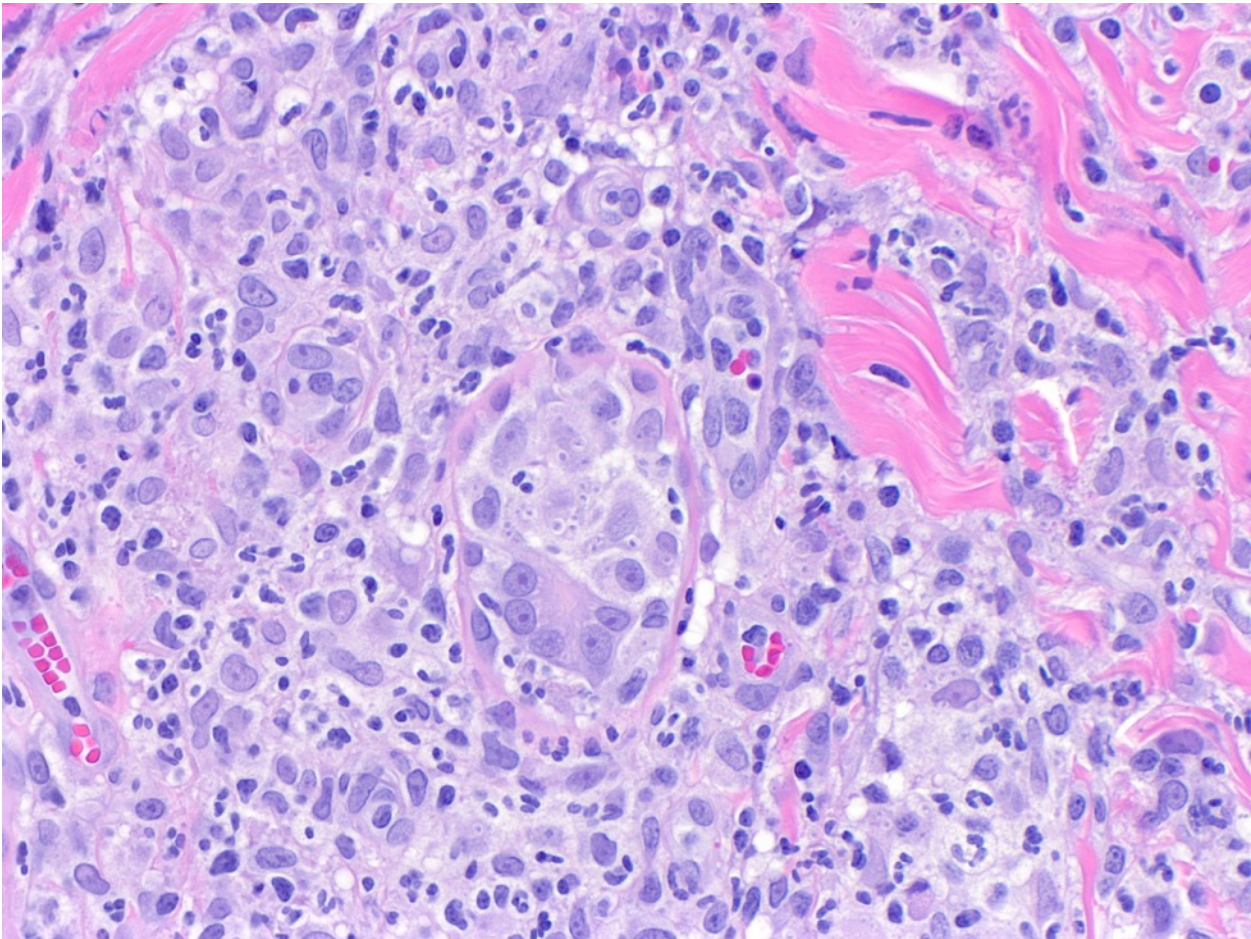
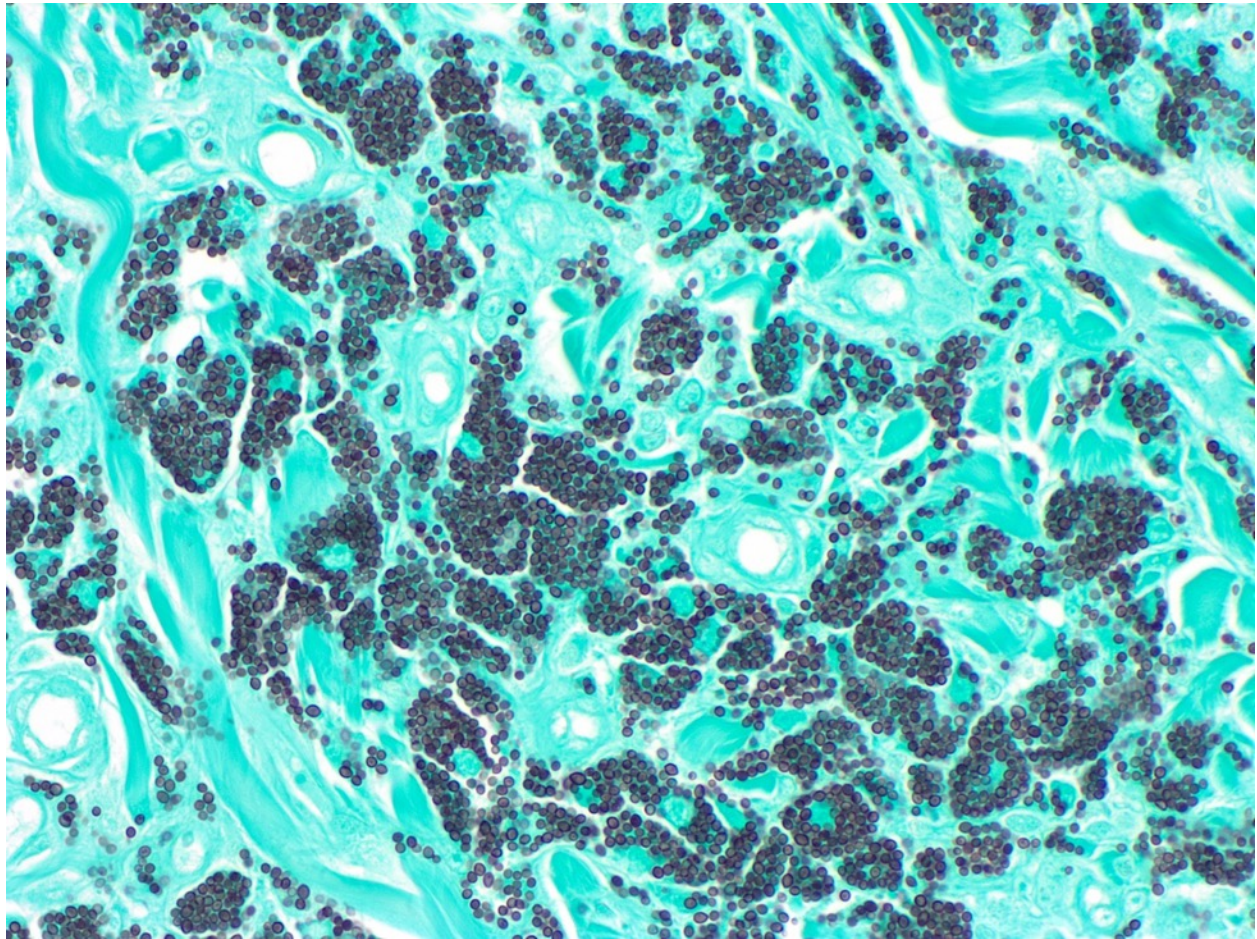


Figure 5: GMS, 200x



Which of the following is the most likely etiology?

- A. *Blastomyces dermatitidis*
- B. *Histoplasma capsulatum***
- C. *Leishmania mexicana*
- D. *Coccidioides immitis*

Histopathologic description

Diffusely infiltrating and expanding the superficial and deep dermis, and extending into the panniculus are multifocal to coalescing, often nodular, areas of dense inflammatory cell infiltration composed of numerous epithelioid macrophages and neutrophils with fewer lymphocytes, plasma cells, and rare multinucleated giant cells. Frequently, within the cytoplasm of macrophages are multiple, round to oval, 2-5 micrometer in diameter, fungal yeasts, with 1-2 micrometer basophilic nuclei surrounded by a 1-2 micrometer peripheral clear zone further enclosed by a thin cell wall (capsule). Similar inflammatory cells, including yeast-laden macrophages, frequently separate and surround folliculosebaceous units and multifocally extend between skeletal muscle fibers in the panniculus. The overlying epidermis is mildly

hyperplastic. On the surface, there is a small amount of orthokeratotic, basketweave and compact parakeratotic keratin.

Morphologic Diagnosis

Haired skin: Marked, diffuse, chronic, granulomatous dermatitis and panniculitis with numerous intrahistiocytic yeast.

Comments

The clinical and microscopic findings are consistent with a diagnosis of cutaneous histoplasmosis. *Histoplasma* sp. is a soil-borne dimorphic fungus that exists in the environment in a mycelial form, producing small microconidia spores and large chlamydospores, and as a yeast-like form within host monocytes and macrophages. Within the United States, histoplasmosis is commonly found in the Ohio River Valley, which includes Mississippi, Ohio, and Missouri; however, its distribution is now much wider, with cases commonly seen further west, including in Texas and Oklahoma. The organisms typically reside in organic matter enriched with bird or bat feces.

Histoplasma sp. can be divided into three species, including *H. capsulatum* var *capsulatum*, *H. capsulatum* var *duboisii*, and *H. capsulatum* var *farciminosum*. The species are associated with distinct diseases, with *H. capsulatum* being the most common cause of histoplasmosis worldwide, *H. var. farciminosum* as the cause of epizootic lymphangitis in equids, and *H. duboisii* as the cause of African histoplasmosis. Unlike var *capsulatum*, var *duboisii* typically causes infections restricted to the skin and subcutis without dissemination to internal organs. While human infections with *H. duboisii* are restricted to regions of Africa, the organism is now endemic within research populations of baboons in Texas.

Numerous domestic and wild mammalian species may be infected, although disease is most frequently reported in dogs and cats. Infection occurs through inhalation or ingestion of microconidia from contaminated soil. When ingested, microconidia reach the lower respiratory tract, where they undergo an incubation period of 12-16 days, during which the spores transform into the parasitic yeast phase and reproduce by narrow-based budding. A similar process is seen within the gastrointestinal tract when the spores are ingested. The host immune system phagocytoses the yeast through the reticuloendothelial system, which then allows the yeast to replicate within the cytoplasm of macrophages and monocytes. Following phagocytosis, hematogenous dissemination to cause systemic disease with possible cutaneous involvement typical. Rarely, *Histoplasma* sp. can be introduced into the skin directly through wound inoculation.

Clinical signs can vary widely between and within species, from asymptomatic to systemic dissemination and eventual death. In cats, the most commonly affected regions are the respiratory system, lymphatics, eyes, and skin. Grossly, the lesions vary depending on the anatomical location, commonly forming numerous miliary nodules within visceral organs. Skin lesions can appear as nodules or multifocal ulcerated to alopecic and thickened areas most commonly around the face and ears. Local lymph nodes are also commonly enlarged. An

important clinical differential in this case is cryptococcosis (*Cryptococcus neoformans*) which classically causes skin lesions in the facial/nasal region of cats, resulting in a “Roman” nose appearance. In this cat, it is unknown if lesions progressed to involve the draining lymph nodes or internal organs.

Microscopically, *Histoplasma* yeast are commonly found within the cytoplasm of macrophages, or can be extracellular within the surrounding tissue. Yeast are round to ovoid and range in size from 2-5 micrometer in diameter with a small round basophilic nucleus surrounded by a clear halo enclosed within a thin cell wall. *Sporothrix schenckii* yeast appear fairly similar, although they typically exhibit a more elongated, “cigar-shaped” appearance. While *Cryptococcus neoformans* yeast usually have a thick, clear capsule resembling a “soap bubble,” an atypical form of cryptococcosis has been described in cats in which yeast are capsular, which represents an important differential in this case. *Blastomyces dermatitidis* yeast are larger (5-20 micrometers) with a double contoured wall and broad-based budding. *Coccidioides immitis* spherules are also larger (20-80 micrometers) with a double contoured wall and exhibit endosporulation. *Leishmania mexicana* is endemic to Texas and can cause cutaneous lesions in cats, typically restricted to the pinnae and/or muzzle. Numerous 2x3 micrometer protozoal amastigotes with a rod-shaped kinetoplast oriented perpendicular to the nucleus can be seen within macrophages. *Leishmania* may be confused with *Histoplasma* based on their similar size and the difficulty in visualizing the kinetoplast on H&E; however, amastigotes will highlight with Giemsa but will be negative with GMS, in contrast to *Histoplasma*.

In cutaneous histoplasmosis, granulomatous to pyogranulomatous inflammatory reaction with macrophages, multinucleated giant cells, and variable numbers of neutrophils is typically evident. While yeasts are typically abundant, in cases where organisms are difficult to identify on H&E, special stains including Periodic Acid-Schiff (PAS) and Grocott’s methenamine silver (GMS) can be pursued to highlight the yeast organisms. GMS is often preferred, as only the nucleus of yeast will stain with PAS.

While the histologic appearance of histoplasmosis is highly characteristic, definitive diagnosis requires fungal culture or PCR. Itraconazole is the typical treatment for disseminated histoplasmosis in dogs and cats, although fluconazole may also be used. A minimum of 6 months of treatment is recommended and relapses are common. Unfortunately, this cat’s skin lesions and respiratory signs worsened despite itraconazole therapy, and he was humanely euthanized.

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Contributors

Haley Dodson, DVM, Department of Veterinary Pathobiology, Texas A&M University, College Station, Texas, USA.

Lauren Stranahan, DVM, PhD, DACVP, Department of Veterinary Pathobiology, Texas A&M University, College Station, Texas, USA.