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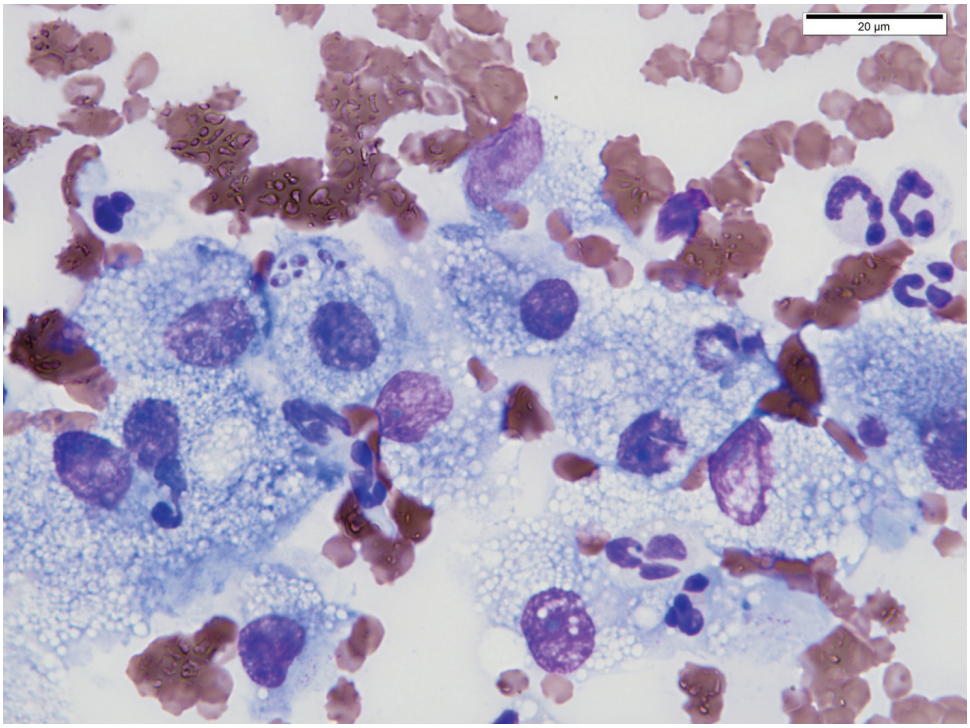

Figure 1—Photomicrograph of a fine-needle aspirate specimen obtained from a pulmonary lesion in a cat with a 1-week history of hyporexia, weight loss (moderate to marked), and respiratory signs. Foamy macrophages and neutrophils are visible on a background of blood. Several microorganisms are observed within a macrophage. Wright-Giemsa stain; bar = 20 µm.

History

A 2-year-old 3.7-kg (8.1-lb) spayed female domestic longhair cat was referred to a veterinary teaching hospital because of a 1-week history of hyporexia, weight loss (moderate to marked; body condition score, 3/9), and respiratory signs. The cat was primarily an outdoor cat and had never traveled outside of Colorado.

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Clinical and Clinicopathologic Findings

Physical examination findings included tachypnea (70 breaths/min) and increased respiratory effort with harsh expiratory lung sounds. Results of a CBC and serum biochemical panel were unremarkable. The cat was negative for anti-FIV antibody and FeLV antigen; no additional evidence of immunosuppression was detected. Thoracic radiography and CT revealed multifocal regions of pulmonary alveolar infiltrates and consolidation. A large gas-attenuating region within the left caudal lung lobe was also observed. Fine-needle aspirate specimens of the infiltrated pulmonary parenchyma were examined cytologically **(Figure 1)**. The specimens were cellular with moderate blood in the background. Many foamy macrophages were present along with low to moderate numbers of neutrophils. Some cells appeared to contain phagocytosed microorganisms.

Formulate differential diagnoses from the history, clinical findings, and Figure 1—then turn the page→

Additional Cytologic and Microbiological Findings

On further examination of the fine-needle aspirate specimens, the organisms in the macrophages and neutrophils were round to oval (maximal dimension, 2 to 4 µm), with a basophilic internal structure and a thin, clear halo **(Figure 2)**. Rarely, these organisms displayed narrow-based budding.

A urine sample was collected via cystocentesis from the cat and submitted to a diagnostic laboratory.[a] An assay to detect *Histoplasma* antigen[b] was performed on the urine sample, and the result was positive (reading was greater than the assay's limit of quantification).

Fungal culture of a lung lesion specimen yielded growth of microorganisms, which were sent to another laboratory[c] for DNA probing. The DNA probing results were negative for *Histoplasma capsulatum* and weakly positive for *Blastomyces dermatitidis*. The fungal isolate underwent DNA sequencing and had 100% identity with *Emmonsia helica* (since reclassified as *Blastomyces helicus*).

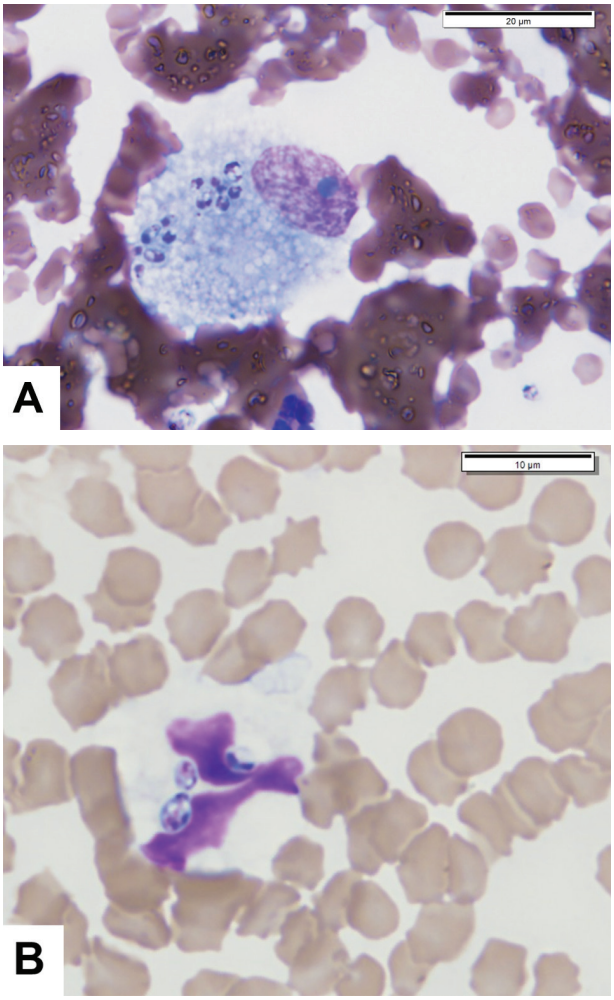

Figure 2—Additional photomicrographs of a fine-needle aspirate specimen obtained from a pulmonary lesion in the cat in Figure 1. A—Notice the phagocytosis by a foamy macrophage of several round to oval microorganisms that have a maximal dimension of 2 to 4 µm. Wright-Giemsa stain; bar = 20 µm. B—A neutrophil contains similar organisms, some of which have narrow-based budding. Wright-Giemsa stain; bar = 10 µm.

Cytologic Interpretation and Case Summary

Cytologic interpretation: pyogranulomatous inflammation of the pulmonary parenchyma with intracellular yeast.

Case summary: *B helicus* pneumonitis in a cat.

Comments

At the referral evaluation, the radiographic and CT findings for the cat of the present report led clinicians to obtain fine-needle aspirate specimens of the infiltrated pulmonary parenchyma for microscopic examination. The cytologic findings directed additional diagnostic testing, which provided a diagnosis of *B helicus* pneumonitis. The cat was treated with itraconazole (10 mg/kg [4.5 mg/lb], PO, q 24 h) for 10 months, at which time treatment was changed because of the owner's financial constraints to fluconazole (13.5 mg/kg [6.1 mg/lb], PO, q 12 h) for an additional 3 months. The total duration of antifungal administration was 13 months. Nine months after diagnosis, a *Blastomyces* antigen assay[d] was performed on a urine sample collected from the cat and the result was negative. A CT scan of the cat was performed 2 years after diagnosis, which revealed marked improvement of the alveolar infiltrates; however, there was evidence of mineralization, fibrosis, and loss of volume in the left lung lobes, all of which were supportive of secondary changes following a chronic inflammatory process. The cat underwent thoracic radiography 3 years after diagnosis, and the radiographic findings corroborated the follow-up CT findings.

The yeast organisms observed were originally suspected to be *H capsulatum* on the basis of morphology alone. As highlighted by the case described in the present report, *B helicus* should be considered an important differential diagnosis when yeast organisms with *H capsulatum*–like morphology are observed in examined specimens. Frequently, a urine antigen assay[b] is the only additional diagnostic test pursued to confirm a cytologic diagnosis of histoplasmosis. The sensitivity and specificity for the detection of *H capsulatum* antigen in feline urine by the *Histoplasma* antigen assay[b] are reported as 92% and 99%, respectively. The sensitivity and specificity of the *Blastomyces* antigen assay[d] for the detection of *B dermatitidis* antigen in urine samples from cats are reported as 90% and 99%, respectively. Specificity appears related to mycoses in general, and the cross-reactivity between these 2 tests for the detection of *H capsulatum* or *B dermatitidis* antigen is nearly 99%.[1] As in the case described in the present report,

it is apparent that the *Histoplasma* antigen assay[b] used can additionally cross-react with *B helicus* antigen, resulting in an erroneous diagnosis of histoplasmosis if specimens had not undergone fungal culture and PCR assay had not been pursued.

The infectious yeast in the case described in the present report was identified as *E helica* and then recently reclassified as *B helicus*.[2] Some of the fungi of the genus *Emmonsia* were reclassified into the genus *Blastomyces* (including *E helica* [reclassified as *B helicus*] and *Emmonsia parva* [reclassified as *Blastomyces parvus*]). Others, such as *Emmonsia crescens*, remained in the genus *Emmonsia*. Prior to speciation and reclassification, the yeast isolated in this case was identified only as *Emmonsia* spp. Fungal infections currently classified as *Emmonsia* infections and those recently reclassified as *Blastomyces* infections can present in 2 distinct manners, as localized adiaspiromycosis or systemic dimorphic yeast. The type of infection may be dependent on the specific species of fungus involved. When first discovered, fungi identified as *Emmonsia* spp were often not further speciated; consequently, reports of *Emmonsia* spp infections could include both the current *Emmonsia* genus and the newly reclassified fungi that fall into the *Blastomyces* genus. These fungi were noted not to replicate during infection but to grow as spherical adiaspores that range from 2 to 4 µm to 40 to 500 µm in diameter and elicit a foreign body reaction.[3]

Adiaspiromycosis appears to most often develop following inhalation of soil conidia.[3,4] It is most commonly observed in small rodents and other small mammals worldwide and is typically identified as infection with *E crescens* or *B parvus* (formerly *E parva*).[3,5] Reports of infection in nonhuman mammals are rare and include reports of adiaspiromycosis in 2 dogs, a goat, a deer, and a horse.[6–10] These affected animals were not apparently immunocompromised, and the disease was an incidental finding at necropsy in most cases. In the horse, the yeast was identified as *E crescens*; in one of the dogs, the yeast was identified as *B parvus*.[6,10] The infective organisms in the other 3 nonhuman animal cases were identified by morphology only as *Emmonsia* spp.[7–9] Adiaspiromycosis in both immunocompetent and immunocompromised humans has been reported,[3,11] although the disease tends to be more severe in immunocompromised individuals.

More recently, disseminated *Emmonsia*-related disease often involving lungs and skin has been described predominantly for immunocompromised humans.[3] In those reported cases,[3] the fungus was dimorphic, replicated in yeast form, and appeared to be an opportunistic infection. The cat of the present report was assessed as immunocompetent. In addition to the present case, isolates of *B helicus* have been associated with pulmonary infections involving 1 other cat and 2 dogs in the western United States.[2] In the cat and one of those dogs, yeast organisms observed in histologic or cytologic specimens were initially mistaken for *H capsulatum*.[2] The immunologic state of the animals in these other *B helicus* cases was unknown.[2] The route of transmission that results in *Emmonsia*-related disease also appears to be inhalation of soil conidia.[2,3] However, definitive determination of the route of transmission in the case described in the present report could not be determined because of the chronicity of the cat's disease. There are no reports of transmission of *Emmonsia* spp or *B helicus* from animal to animal, human to animal, or animal to human. Thus, adiaspiromycosis and disseminated *Emmonsia*-related disease are not suspected to be of zoonotic concern, although both nonhuman animals and humans can be infected by both disease forms.

Emmonsia spp and *B helicus* are most closely related to *B dermatitidis* and *H capsulatum*.[3] This relationship was likely the reason that the *Histoplasma* antigen assay yielded a positive result and the DNA probing for *Blastomyces* yielded a weakly positive result for the cat of the present report. Morphologically, *Emmonsia* yeast forms have been mistaken for both *B dermatitidis* and *H capsulatum* on histologic examination and culture of specimens.[3] In the case described in the present report, it should be noted that the cytologic appearance of *B helicus* was very different from that of *B dermatitidis* but similar to that of *H capsulatum*. In other instances, the histologic appearance of large *Emmonsia* adiaspores has been confused with that of *Coccidioides* spp.[12]

Emmonsia adiaspores do not grow well in culture, and diagnosis is often dependent on morphological features or PCR assay results. However, yeast forms of *Emmonsia* generally grow well in culture and can subsequently be identified with a PCR assay.[3] The nomenclature of *Emmonsia* fungi has varied, with genus names including *Haplosporangium* and *Chrysosporium* in addition to *Emmonsia* and *Blastomyces*.[11] No obvious misclassifications of *Emmonsia*-related adiaspiromycosis or disseminated disease in domestic veterinary species associated with either of the previous genera (*Haplosporangium* and *Chrysosporium*) were discovered upon the authors' review of published literature. The reclassification of *E helica* and *E parva* as *B helicus* and *B parvus*, respectively, should be noted for future investigation of veterinary cases involving fungal infections of this description.

Differentiation of *B helicus* infections from *H capsulatum* infections may be important to help elucidate the true prevalence of *B helicus* infection. It is possible that the infrequent reports of *B helicus* infection are attributable to the organisms' similarity to other more well-known fungi, such as *H capsulatum*, rather than to a low prevalence of infection. Moreover, understanding differences between infections with these 2 fungal organisms in regard to prognosis, response to treatment, and risk factors for infection (including geographic distribution and animal species affected) would be valuable.

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Footnotes

a. MiraVista Diagnostics, Indianapolis, Ind.
b. MiraVista *Histoplasma* antigen assay, MiraVista Diagnostics, Indianapolis, Ind.
c. Fungus Testing Laboratory, University of Texas Health Science Center at San Antonio, San Antonio, Tex.
d. MiraVista *Blastomyces* antigen assay, MiraVista Diagnostics, Indianapolis, Ind.

References

1. MiraVista Veterinary Diagnostics. *Histoplasma* antigen assay and *Blastomyces* antigen assay sensitivity, specificity, and cross-reactivity. Indianapolis: MiraVista Veterinary Diagnostics, 2018.
2. Schwartz IS, Wiederhold NP, Hanson KE, et al. *Blastomyces helicus*, a new dimorphic fungus causing fatal pulmonary and systemic disease in humans and animals in Western Canada and the United States. *Clin Infect Dis* 2019;68:188–195.
3. Schwartz IS, Kenyon C, Feng P, et al. 50 Years of *Emmonsia* disease in humans: the dramatic emergence of a cluster of novel fungal pathogens. *PLoS Pathog* 2015;11:e1005198.
4. Sigler L. Adiaspiromycosis and other infections caused by *Emmonsia* species. In: Hay RJ, Merz WG, eds. *Topley and Wilson's microbiology and microbial infections.* 10th ed. London: Arnold Hodder, 2005;809–824.
5. Borman AM, Simpson VR, Palmer MD, et al. Adiaspiromycosis due to *Emmonsia crescens* is widespread in native British mammals. *Mycopathologia* 2009;168:153–163.
6. al-Doory Y. Adiaspiromycosis in a dog. *J Am Vet Med Assoc* 1971;159:87–90.
7. Koller LD, Patton NM, Whitsett DK. Adiaspiromycosis in the lungs of a dog. *J Am Vet Med Assoc* 1976;169:1316–1317.
8. Koller LD, Helfer DH. Adiaspiromycosis in the lungs of a goat. *J Am Vet Med Assoc* 1978;173:80–81.
9. Matsuda K, Niki H, Yukawa A, et al. First detection of adiaspiromycosis in the lungs of a deer. *J Vet Med Sci* 2015;77:981–983.
10. Pusterla N, Pesavento PA, Leutenegger CM, et al. Disseminated pulmonary adiaspiromycosis caused by *Emmonsia crescens* in a horse. *Equine Vet J* 2002;34:749–752.
11. Anstead GM, Sutton DA, Graybill JR. Adiaspiromycosis causing respiratory failure and a review of human infections due to *Emmonsia* and *Chrysosporium* spp. *J Clin Microbiol* 2012;50:1346–1354.
12. Emmons CW, Jellison WL. *Emmonsia crescens* Sp. N. and adiaspiromycosis (haplomycosis) in mammals. *Ann N Y Acad Sci* 1960;89:91–101.