

ORIGINAL ARTICLE

A Dimorphic Fungus Causing Disseminated Infection in South Africa

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ABSTRACT

BACKGROUND

The genus *emmonsia* contains three species that are associated with human disease. *Emmonsia crescens* and *Emmonsia parva* are the agents that cause adiaspiromycosis, and one human case of *Emmonsia pasteuriana* infection has been described. We report a fungal pathogen within the genus *emmonsia* that is most closely related to *E. pasteuriana* in human immunodeficiency virus (HIV)-infected adults in South Africa.

METHODS

Between July 2008 and July 2011, we conducted enhanced surveillance to identify the cause of systemic, dimorphic fungal infections in patients presenting to Groote Schuur Hospital and other hospitals affiliated with the University of Cape Town, Cape Town, South Africa. DNA sequencing was used to identify pathogenic fungi.

RESULTS

A total of 24 cases of dimorphic fungal infection were diagnosed, 13 of which were caused by an *emmonsia* species. All 13 patients were HIV-infected, with a median CD4+ T-cell count of 16 cells per cubic millimeter (interquartile range, 10 to 44), and all had evidence of disseminated fungal disease. Three patients died soon after presentation, but the others had a good response to a variety of antifungal agents and antiretroviral therapy. Phylogenetic analysis of five genes (*LSU*, *ITS1-2*, and the genes encoding actin, β -tubulin, and intein PRP8) revealed that this fungus belongs in the genus *emmonsia* and is most closely related to *E. pasteuriana*.

CONCLUSIONS

The findings suggest that these isolates of an *emmonsia* species represent a new species of dimorphic fungus that is pathogenic to humans. The species appears to be an important cause of infections in Cape Town.

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THE HUMAN IMMUNODEFICIENCY VIRUS (HIV) pandemic in sub-Saharan Africa has resulted in an epidemic of opportunistic fungal diseases, some of which are caused by new and emerging fungal pathogens.¹ Much remains to be learned about the endemic fungi of sub-Saharan Africa. For example, considerable differences have been noted between the African and North American varieties of *Histoplasma capsulatum* and *Blastomyces dermatitidis*.² The genus *emmonsia* contains three species associated with human disease. *Emmonsia crescens* and *Emmonsia parva* are the agents of adiaspiromycosis, a pulmonary disease of small mammals and occasionally of humans.³ *Emmonsia pasteuriana* infection has been described in a single human case — that of an Italian patient with late-stage acquired immunodeficiency syndrome — but has not been found in any animal or environmental sources.⁴ Here we report on a series of 13 HIV-infected adults in South Africa with disseminated infection caused by a thermally dimorphic, opportunistic fungal pathogen within the genus *emmonsia* that is most closely related to *E. pasteuriana*.

METHODS

SURVEILLANCE METHODS AND CASE DEFINITION

From July 2008 through July 2011, we used an enhanced surveillance system to identify the cause of systemic dimorphic fungal infections in patients presenting to Groote Schuur Hospital and other hospitals affiliated with the University of Cape Town, Cape Town, South Africa. Up to 30% of adults are HIV-infected in the communities served by these hospitals.⁵ Cases were defined by evidence of a thermally dimorphic fungus cultured from a normally sterile site (e.g., blood, cerebrospinal fluid, or skin tissue), in addition to histologic evidence of a deep fungal infection and a clinical syndrome compatible with a disseminated fungal infection. Clinicians were encouraged to submit appropriate specimens for culture and histologic analysis in all cases of suspected disseminated fungal infection. The ability to detect and characterize dimorphic fungi was also strengthened during this time at the clinical diagnostic laboratory at Groote Schuur Hospital. This included more careful phenotypic descriptions of the fungi and the introduction of a broad-range fungal polymerase-chain-reaction (PCR) assay, which allowed molecular identification of all fungi at the species level.

In addition, fungal isolates were submitted to the Mycology Reference Laboratory at the National Institute for Communicable Diseases for phenotypic and genotypic characterization.

We collected clinical and laboratory data on all 13 patients with disseminated *emmonsia* disease and other dimorphic fungal infections that were diagnosed during this period. We also performed a retrospective search for all cases of dimorphic fungal disease diagnosed between March 2003 and July 2011. First, we searched the laboratory electronic database for all skin-biopsy histologic reports that provided evidence of deep fungal invasion by using the keywords “fungi” and “fungal.” Deep fungal invasion was defined as fungi visible in the dermis. Second, we searched the laboratory database for all dimorphic fungi cultured in the microbiology laboratory during the same period. The study was approved by the Human Research Ethics Committee of the University of Cape Town.

LABORATORY PROCEDURES

Details of the specimen collection, culture, determination of antifungal sensitivity, DNA sequence-based methods, and microscopical studies are given in Section S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

RESULTS

IDENTIFICATION OF CASES

The review of the skin-biopsy histologic results for the 8-year period revealed 62 cases of deep fungal infection. A total of 39 of the 62 cases (63%) were histologically classified as histoplasmosis, but a dimorphic fungus was cultured from skin-biopsy or blood specimens in only 24 of these 39 cases (62%). Of the 24 fungi, 4 (17%) morphologically resembled *H. capsulatum* (3 cultured from skin-biopsy specimens and 1 cultured from a blood specimen). Only 1 of the isolates was genotypically confirmed as *H. capsulatum*. The other 20 fungi were identified as *emmonsia* species (10 fungi), *Sporothrix schenckii* (4), cryptococcus species (3), and candida species (3). During the enrollment period, 2 additional cases of *emmonsiosis* were diagnosed at a neighboring laboratory in Cape Town and 1 at a hospital in Bloemfontein, South Africa. We include these 3 cases in our case series. In addition to the isolates of *emmonsia* (10 fungi), *histoplasma* (4), and *sporothrix* (4) that

Table 1. Clinical Characteristics and Laboratory Results for 13 HIV-Infected Patients with Disseminated <i>Emmonsia</i> Infection.*	
Variable	Value
Clinical characteristics — no./total no. (%)	
Night sweats	4/13 (31)
Fever	12/13 (92)
Loss of weight	10/13 (77)
Lymphadenopathy	3/13 (23)
Hepatomegaly or splenomegaly	1/13 (8)
Skin lesions	13/13 (100)
Anemia	13/13 (100)
Chest radiograph compatible with pulmonary tuberculosis	11/13 (85)
Laboratory results	
CD4+ T-cell count nadir — cells/mm ³	
Median	16
Interquartile range	10–44
CD4+ T-cell count <100 cells/mm ³ — no./total no. (%)	12/13 (92)
Creatinine — μmol/liter	
Median	71
Interquartile range	52–88
Reference range	49–90
Total bilirubin — μmol/liter	
Median	15
Interquartile range	11–22
Reference range	0–21
Conjugated bilirubin — μmol/liter	
Median	16
Interquartile range	11–24
Reference range	0–5
Alkaline phosphatase — U/liter	
Median	129
Interquartile range	109–183
Reference range	40–120
γ-Glutamyl transferase — U/liter	
Median	142
Interquartile range	112–261
Reference range	0–35
Alanine aminotransferase — U/liter	
Median	51
Interquartile range	37–68
Reference range	5–40

Table 1. (Continued.)	
Variable	Value
Aspartate aminotransferase — U/liter	
Median	143
Interquartile range	117–194
Reference range	5–40
Elevated γ-glutamyl transferase or alkaline phosphatase — no./total no. (%)	
	8/9 (89)
Hemoglobin — g/liter	
Median	9
Interquartile range	7–9
Reference range	12–15
White-cell count — $\times 10^9$/liter	
Median	5
Interquartile range	3–8
Reference range	4–10
Neutrophil count — $\times 10^9$/liter	
Median	2.9
Interquartile range	2.4–7.6
Reference range	2.0–7.5
Lymphocyte count — $\times 10^9$/liter	
Median	0.8
Interquartile range	0.5–1.2
Reference range	1.0–4.0
Monocyte count — $\times 10^9$/liter	
Median	0.3
Interquartile range	0.1–0.5
Reference range	0.2–0.8
Platelet count — $\times 10^9$/liter	
Median	257
Interquartile range	205–363
Reference range	178–400
Positive specimen on direct examination — no./total no. (%)	
Peripheral blood	1/13 (8)
Urine	0/7
Sputum	0/9
Positive specimen on culture — no./total no. (%)	
Blood	5/11 (45)
Cerebrospinal fluid	0/3
Skin-biopsy specimen	9/9 (100)
Sputum	0/4

* Fever was defined as a body temperature of more than 38°C. Anemia was defined as a hemoglobin level of less than 12 g per deciliter. To convert the values for creatinine to milligrams per deciliter, divide by 88.4. To convert the values for bilirubin to milligrams per deciliter, divide by 17.1.

were both cultured and visible on skin biopsy, the microbiology laboratory cultured dimorphic fungi from specimens obtained from 6 other cases of fungal infection in this 8-year period — all *S. schenckii*. All the diagnoses of emmonsia species infection were made after the introduction of our broad-range fungal PCR assay in July 2008 (Fig. S1 in the Supplementary Appendix).

CLINICAL FEATURES OF THE 13 PATIENTS WITH EMMONSIA SPECIES INFECTION

The median age of the patients was 34 years (interquartile range, 29 to 38). Eight of the 13 patients were men. All 13 presented with evidence of clinically advanced HIV disease and with very low CD4+ T-cell counts (median, 16 cells per cubic millimeter; interquartile range, 10 to 44). All the patients were anemic, and all had widespread skin lesions. Morphologically, these lesions varied from erythematous papules and plaques with or without scales to ulcers and crusted, boggy plaques. The larger plaques and ulcers healed with marked scarring, and the smaller lesions healed with residual hyperpigmentation. Mucosal ulceration of the penis was noted in 1 patient, and 1 patient had scaly papules on the lips. The lesions in 2 patients showed evidence of central necrosis, and in 1 patient there was evidence of central umbilication. Further details of the clinical presentation and pathological results are shown in Table 1 and Figure 1, and in Table S1 in the Supplementary Appendix.

Antituberculosis treatment was started in six patients in the 3 months preceding hospitalization and in three patients during hospitalization. Tuberculosis was confirmed in only two of these patients. Most patients had dramatic and rapid responses to amphotericin B deoxycholate at a dose of 1 mg per kilogram of body weight per day for 14 days, followed by itraconazole maintenance therapy. (For information on other antifungal treatments, see Table S1 in the Supplementary Appendix.) In most patients, the skin lesions healed almost completely, weight increased, and exercise tolerance returned to near-baseline levels. Five patients were receiving antiretroviral therapy (ART) at the time of presentation. Two of these patients had virologic and immunologic failure; the other three patients, who presented 4, 7, and 11 weeks after starting ART, had a more pronounced mixed inflammatory infiltrate in the dermis than the patients not receiving ART. One patient had evidence of dermal microabscesses.

ART was started in the remaining eight patients soon after they started itraconazole, without complications. Three patients died — all soon after the diagnosis of emmonsiosis was made. One patient, with numerous yeasts visible on the peripheral-blood smear (Fig. S2 in the Supplementary Appendix), died before definitive antifungal therapy was commenced, and two died before they completed the 14-day course of amphotericin B. One patient was lost to follow-up at 3 months; the other patients were followed for a mean of 19 months.

MYCOLOGIC CHARACTERISTICS OF THE EMMONSIA SPECIES

The fungi grown from all 13 patients were very similar morphologically.

Mycelial Phase

Pure, single-conidium subcultures were obtained from primary cultures grown on Sabouraud's dextrose agar, incubated at 25°C in the dark. In general, colonies grew at a slow-to-moderate rate, reaching a diameter of 15 to 25 mm after 7 to 14 days, up to a maximum of 50 to 60 mm in 21 days. They appeared glabrous in some early cultures or showed densely white growth, taking on a folded, wrinkled, or cerebriform appearance, and became light brown with powdery segments over time (Fig. 2A). Cultures grew well at 30°C on both Sabouraud's dextrose agar and brain-heart infusion agar, forming slightly larger colonies as compared with those grown at 25°C. No diffusible pigment was noted, and the reverse side of the colonies was either tan or yellow-brown, with darker brown pigment in the folds or groves of older colonies (Fig. 2A). None of the strains grew at 40°C, and no adiaspores were produced at this temperature.

On light microscopy, preparations showed septate, hyaline hyphae, 1 to 1.2 μm in diameter, with numerous smooth-walled conidia that were oval to subglobose. Conidia were borne on thin pedicles (0.4 to 0.5 μm wide) that formed perpendicular to an ampulliform vesicle (Fig. 2B). These vesicles gave rise to single pedicles at first, then four to eight pedicles, each forming a terminal conidium, establishing a "floret" of four to eight conidia grouped together (Fig. 2B). Conidia were attached to the pedicles by their long axes, appearing flattened on top with slightly roughened walls after 21 to 30 days (Fig. 2B). Scanning electron microscopy confirmed these features



Figure 1. Clinical Features of *Emmonsia* Species Infection.

Shown are crusted, boggy facial plaques and nodules on one patient before treatment (Panel A) and 1 month after the start of treatment (Panel B). Another patient presented with generalized scaly and erythematous papules a few millimeters in diameter (Panels C and D).

and showed that the mature conidia had distinctly tuberculated cell walls (Fig. 2D). Smooth-walled, immature conidia measured 1 to 2 μm by 1.5 to 2.0 μm (Fig. 2C), and mature conidia with tuberculated cell walls were 1 to 2 μm by 1.5 to 2.5 μm (Fig. 2D). No adiaspores were seen in any of the cultures incubated at 37°C or 40°C.

Yeast Phase

Mycelial cultures were converted to the yeast phase by incubating streaked or single-colony subcultures on brain–heart infusion agar at 37°C after 10 to 14 days. Yeast colonies appeared smooth, with a cream-to-beige color that became light brown with age (Fig. 2E). Light mi-

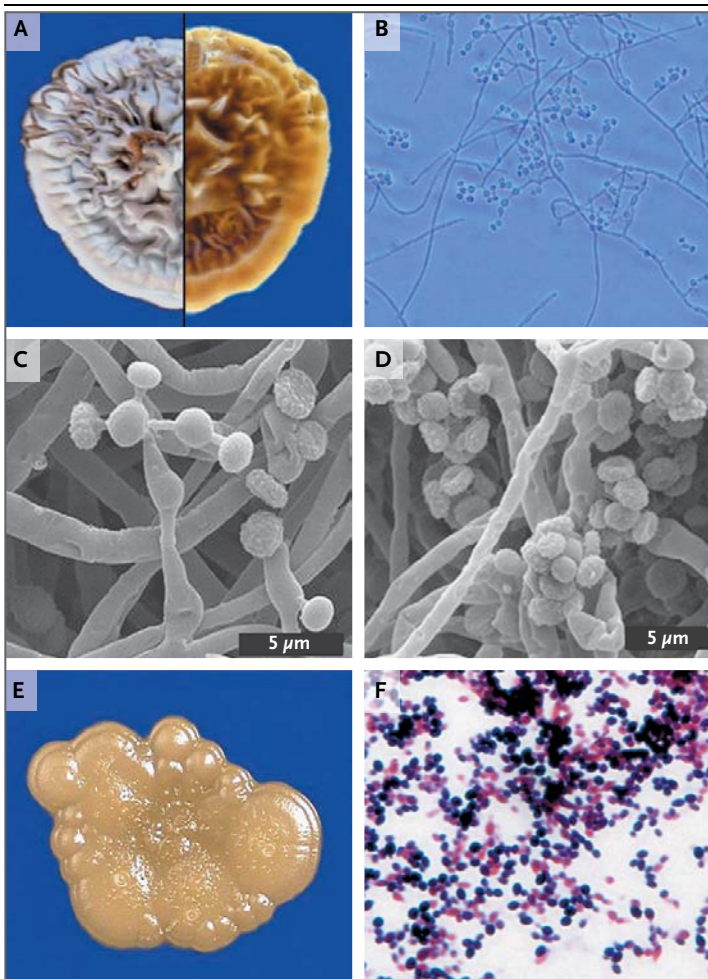


Figure 2. Macroscopic and Microscopical Features of the Cultured Isolates.

Panel A shows filamentous growth on Sabouraud's dextrose agar at 25°C: the top surface of the colony (left half) is cerebriiform and powdery, and the bottom surface (right half) is pigmented. Panel B shows a light-microscopic image of filamentous growth: hyaline, smooth-walled, subglobose conidia, borne singularly at the ends of narrow pedicles, are arranged either singularly or in groups around swollen vesicles at right angles along the hyphae or terminally and are flattened along the longitudinal axis (lactophenol cotton-blue stain). Panel C shows a scanning electron-microscopical image of young, ovoid conidia with smooth cell walls borne on thin, single denticles. Panel D shows a scanning electron-microscopical image of mature "florets" of conidia with cell-wall ornamentations. Panel E shows a yeast colony grown on brain–heart infusion agar at 37°C. Panel F shows gram-positive globose or oval yeasts with single or multiple narrow-base budding.

croscopy revealed small, thin-walled, globose-to-oval yeasts (2 to 4 μm in diameter), with mostly single, but occasionally multiple, polar budding yeasts formed from a narrow base attachment (Fig. 2F).

The macroscopic and microscopical features of these isolates were indistinguishable from

those of *E. pasteuriana*. The histologic findings are shown in Figure S3 in the Supplementary Appendix.

SUSCEPTIBILITY TO ANTIFUNGAL AGENTS

Minimum inhibitory concentrations were determined for six isolates and the type strain (Table S2 in the Supplementary Appendix). The values were higher (i.e., susceptibility was lower) for the echinocandins and flucytosine than for the triazoles and amphotericin B.

MOLECULAR IDENTIFICATION

Sequence analysis of large-subunit ribosomal DNA (LSU), internal transcribed spacer (ITS1-2) ribosomal DNA (rDNA) regions, and portions of the genes encoding β -tubulin, actin, and intein PRP8 confirmed that all 12 isolates that were tested belonged to a distinct (and homogeneous) cluster (Fig. 3, and Fig. S4 in the Supplementary Appendix). The isolate of one patient was not available for sequencing. *E. pasteuriana* (National Collection of Pathogenic Fungi [NCPF] strain 4236) was the closest genetic and morphologic relative to this new cluster.

DISCUSSION

Through DNA sequence–based methods, we have identified a cluster of cases of disseminated fungal infection in severely immunosuppressed HIV-infected patients, caused by a thermally dimorphic, opportunistic fungal pathogen within the genus *Emmonsiopsis* that is most closely related to *E. pasteuriana*. The infection was fatal in three patients.

The chest radiographic findings mimicked those associated with tuberculosis in the majority of cases (11 of 13, 85%), and skin lesions were considered to be suggestive of a disseminated fungal infection by the initial attending doctors in only a minority of cases. The skin lesions were easily confused with lesions due to several more common nonfungal diseases (Table S1 in the Supplementary Appendix). They were morphologically indistinguishable from lesions that are characteristic of other prevalent dimorphic fungal infections — the broad-based cutaneous lesions were similar to those of sporotrichosis, and the fine miliary lesions were akin to those of disseminated histoplasmosis.

These considerations highlight the importance of tissue biopsy in the diagnosis of deep fungal

disease. Emmonsiosis was diagnosed only in patients with extensive skin lesions, and it is possible that infected patients who had extracutaneous manifestations without skin involvement, such as pulmonary or hepatic disease, were not identified. Of note, eight of nine patients who underwent liver-function tests (89%) had elevated alkaline phosphatase or γ -glutamyltransferase levels, findings suggestive of hepatic infiltration. Three of five patients who presented after starting ART had findings compatible with an unmasking immune reconstitution inflammatory syndrome — that is, they had histologic evidence of a more pronounced mixed inflammatory infiltrate in the dermis, including one patient who had microabscesses in the dermis.

There are only two reports in the literature of infections with emmonsia species other than *E. parva* and *E. crescens*. In the first case, a progressive pneumonic illness developed in a farmer in Germany receiving long-term glucocorticoid therapy.⁶ A thermally dimorphic fungus was grown from a transbronchial-biopsy specimen. No asexual spores were seen in biopsy specimens or in specimens obtained later, during partial pneumectomy, but numerous yeasts were positive on periodic acid–Schiff staining. Sequencing of the 18S rDNA region revealed that the fungus was an emmonsia species. The second case involved an Italian woman with advanced HIV infection, who was not receiving ART and who presented with emaciation, vomiting, and numerous skin lesions.⁴ Skin-biopsy cultures grew the dimorphic fungus *E. pasteuriana*.

During the 3-year period after the introduction of a broad-range fungal PCR assay, we diagnosed 13 cases of disseminated infection with this newly identified emmonsia species, and diagnoses of culture-confirmed histoplasmosis declined by a commensurate amount (Fig. S1 in the Supplementary Appendix). This suggests that the infection may have been misdiagnosed for an undetermined period. This inference is supported by the description of the NCPF 4164 isolate, obtained in 1995 from a South African HIV-infected patient described as having “extensive folliculitis,” which is genetically indistinct from the more recent isolates that we describe here.

Four aspects of the phylogenetic analyses suggest that these isolates represent a new emmonsia species. First, the African clade is supported by four of five individual gene trees. The

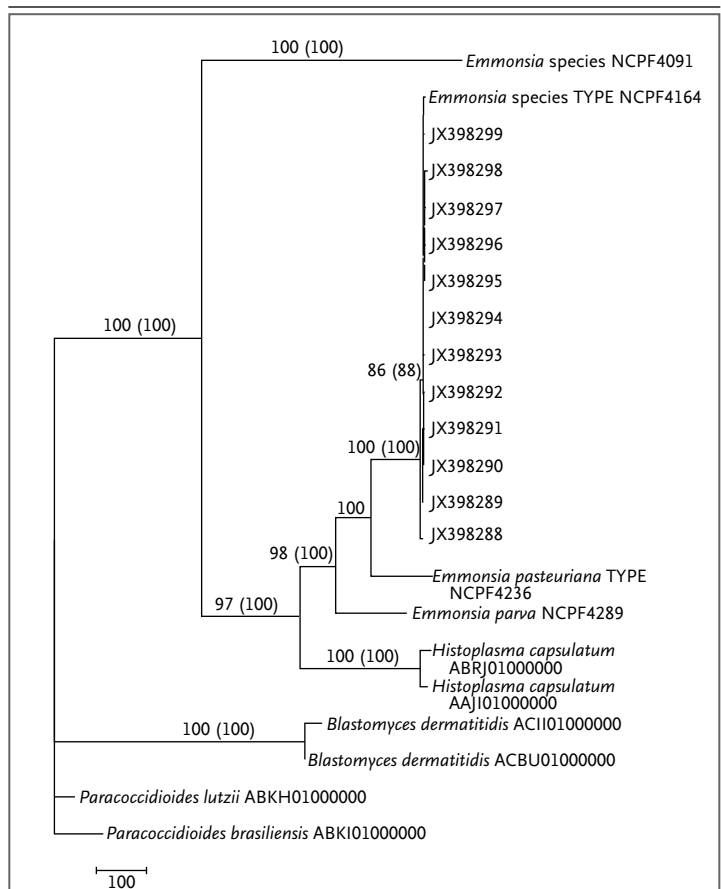


Figure 3. Phylogenetic Analyses of *Emmonsia* and Related Genera.

This diagram depicts the phylogeny of emmonsia and related genera as determined by the concatenated data for five genes: internal transcribed spacer (*ITS1-2*) ribosomal DNA regions, large-subunit ribosomal RNA (*LSU*), and the genes encoding intein PRP8, β -tubulin, and actin. The numbers of positions analyzed were as follows: *ITS1-2*, 586; *LSU*, 358; intein PRP8, 776; β -tubulin, 654; and actin, 524. A more detailed description of the methods is provided in Section S1 in the Supplementary Appendix. The five trees for the individual genes are shown in Figure S4 in the Supplementary Appendix. In all five trees, the clinical cases described in this report from South Africa grouped together in a well-supported clade (JX398288 to JX398299). Sequences are identified by their GenBank accession numbers. The scale bar corresponds to the number of substitutions per site. The Bayesian results are included in parentheses after the bootstrap values. For sequences obtained from GenBank, the accession number is shown; for those obtained from the National Collection of Pathogenic Fungi, in the United Kingdom, the NCPF number is shown. Sequences for paracoccidioides, blastomyces, and histoplasma were obtained from publicly available whole-genome sequences for these organisms. The European Molecular Biology Laboratory (EMBL) accession numbers for the five loci for NCPF strains 4164, 4236, 4289, and 4091 are HF 563662 through HF 563681.

bootstrap values for *ITS1-2* and the genes encoding intein PRP8, β -tubulin, and actin were 100, 100, 100, and 82, respectively. The value on Bayesian analysis was 100 for each of these four loci. The

emmonsia tree for *LSU*, which has a slow evolutionary rate of substitution, included the two species *E. pasteuriana* and *E. parva*. Second, genetic isolation appears to be absolute, because no incongruities were detected between the African isolates and *E. pasteuriana* in the five genealogies studied. Third and most important, the African isolates cluster tightly together in the concatenated phylogenetic tree, with a bootstrap value of 100 and a Bayesian value of 100. Fourth, the African isolates differed from their closest relative, *E. pasteuriana*, at 218 positions within the total 2720 base pairs sequenced (8.0% overall divergence, with nucleotide identities for *LSU*, *ITS1-2*, and the genes encoding actin, β -tubulin, and intein PRP8 of 99.7%, 93.1%, 93.7%, 93.1%, and 85.1%, respectively), as compared with a divergence of 4.8% (134 of 2774 base pairs) for the same loci between the sister species *Paracoccidioides brasiliensis* and *P. lutzii*, which last shared a com-

mon ancestor 32 million years ago⁷ (nucleotide identities for *LSU*, *ITS1-2*, and the genes encoding actin, β -tubulin, and intein PRP8 of 99.4%, 94.8%, 91.0%, 98.5%, and 93.7%, respectively). Despite these findings, further investigations are necessary before it can be concluded that this emmonsia species represents a new species.

Recognizing this emmonsia species as an emerging dimorphic fungus raises issues concerning the handling of specimens in the laboratory. We currently handle the species as we would handle Advisory Committee on Dangerous Pathogens (ACDP) Hazard Group 3 pathogens, such as *H. capsulatum*, *B. dermatitidis*, and *Penicillium marneffei*.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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