

# First Human Case of Pulmonary Fungal Ball Due to a *Perenniporia* Species (a Basidiomycete)

Anuradha Chowdhary,<sup>a</sup> Kshitij Agarwal,<sup>b</sup> Shalu Kathuria,<sup>a</sup> Pradeep Kumar Singh,<sup>a</sup> P. Roy,<sup>a</sup> S. N. Gaur,<sup>b</sup> Anderson M. Rodrigues,<sup>c</sup> G. S. de Hoog,<sup>c</sup> and Jacques F. Meis<sup>d,e</sup>

Departments of Medical Mycology<sup>a</sup> and Pulmonary Medicine,<sup>b</sup> Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, India; CBS-KNAW Fungal Biodiversity Centre, Utrecht, The Netherlands<sup>c</sup>; Department of Medical Microbiology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands<sup>d</sup>; and Department of Medical Microbiology and Infectious Diseases, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands<sup>e</sup>

***Perenniporia* species are basidiomycetes, resupinate shelf fungi responsible for white rot decay of wood. Here, we report for the first time an intracavitary pulmonary fungal ball due to a species of *Perenniporia* that has not been recognized so far as a human pathogen. The fungus was identified by sequencing of the partial ribosomal operon of a culture from a clinical specimen.**

## CASE REPORT

A 55-year-old nonsmoking male from Assam, India, presented with complaints of intermittent right-sided nonanginal chest pain and 5 to 6 episodes of minor hemoptysis over a period of 1 month. The patient gave a history of having received antitubercular therapy 3 years before with a 6-month-long regimen containing rifampin, isoniazid, ethambutol, and pyrazinamide for sputum-smear-positive pulmonary tuberculosis, with which he had been compliant until declared cured by his physician. The patient was found to have uncontrolled diabetes mellitus as revealed by an HbA<sub>1c</sub> level of 13%. He was previously evaluated in Assam, where a chest radiograph showed a cavity in the right upper and middle pulmonary zone. A contrast-enhanced computerized tomography (CECT) scan of his thorax revealed the presence of fibroparenchymal lesions with mild traction bronchiectasis in the right lung (sequelae of healed pulmonary tuberculosis) associated with a fungal ball in the right lower lobe (Fig. 1). The patient was treated with CT-guided percutaneous intracavitary injection of amphotericin B, though records of the dosing schedule could not be obtained. The patient was then referred to Delhi for mycological diagnosis and further management of the case. The patient underwent a fiber optic bronchoscopy (FOB) to rule out the possibility of reactivation of tuberculosis and for an investigative work-up for hemoptysis. The FOB showed no endobronchial lesion, active bleeding, or blood clots in the bronchi. A diagnostic bronchoalveolar lavage (BAL) fluid sample was taken from the apical segment of the right lower and postero-anterior basal segment of the right upper lobe.

**Mycological investigations.** Direct microscopy of KOH wet mounts of the BAL fluid specimen revealed hyaline septate hyphae (Fig. 2A). Cultures yielded multiple white, cottony colonies of identical molds on Sabouraud's glucose agar (SGA) plates incubated for 7 days at 28°C and 37°C. Subcultures on potato dextrose agar (PDA) incubated at 28°C and 37°C showed dense white cottony growth after 7 days (Fig. 2B), and slide cultures of the mold isolates on PDA at 28°C revealed hyaline septate hyphae with chlamydospore-like cells (Fig. 2C). No clamp connections or hyphal pegs were seen during up to 3 weeks of incubation. The isolate was assigned accession no. VPCI 85/P/10 (CBS 130020) for molecular identification and antifungal susceptibility testing. BAL fluid was also investigated microscopically after Gram and Ziehl-Neelsen

(ZN) staining and cultured for aerobic pathogens and *Mycobacterium* spp. The Gram and ZN stains were negative, and cytology was negative for any malignant cells. No *Mycobacterium* spp. were isolated after 6 weeks of incubation.

Immunodiffusion of the patient's serum demonstrated precipitins against culture filtrate antigen prepared from the patient's isolate as described previously (Fig. 2D) (3, 4). In contrast, negative results were found in tests using antigens of *Aspergillus fumigatus*, *Aspergillus flavus*, *Aspergillus terreus*, and *Aspergillus niger*. It was evident from these findings that the patient was suffering from posttuberculosis fibrocavitary disease of the right lobe with a fungal ball. Since no episodes of hemoptysis in the recent past were reported by the patient, no active intervention was done and he was managed conservatively on an outpatient basis. He was briefed about the possibility of recurrent episodes of hemoptysis, for which he was prescribed ethamsylate and cough suppressants, and was advised to consult a nearby medical facility for the same in his hometown in Assam.

The identification of 85/P/10 (CBS 130020) was done by sequencing of the internal transcribed spacer (ITS) ribosomal DNA (rDNA) region and D1/D2 large subunit (LSU) regions as described previously (3, 4). GenBank BLAST searches were performed for species identification. The LSU sequence of CBS 130020 showed 99% identity with *Megasporoporia setulosa* GU566007 (strain MG38) and 100% identity with an unidentified *Perenniporia* species, strain 1V2/2 (GQ982883). The ITS region sequence of the isolate exhibited 100% identity with the *Perenniporia* strain 1V2/2 (GQ982890). The nearest neighbor, *Megasporoporia setulosa* JF894111, showed 90% similarity. The ITS and LSU nucleotide sequences for the isolate CBS 130020 were deposited in GenBank under the accession numbers JX271779 and JX292098, respectively.

ITS sequences from reference isolates belonging to the genera

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Address correspondence to Anuradha Chowdhary, dranuradha@hotmail.com.

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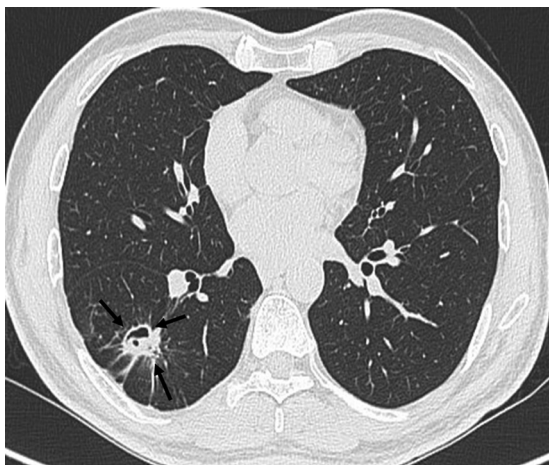


FIG 1 High-resolution CECT scan of the patient showing a fungal ball within a cavity located in the lower lobe of the right lung (arrows).

*Abundisporus* ( $n = 5$ ), *Agaricomycetes* ( $n = 2$ ), *Donkioporia* ( $n = 1$ ), *Megasporoporia* ( $n = 6$ ), *Microporellus* ( $n = 1$ ), *Perenniporia* ( $n = 53$ ), *Perenniporiella* ( $n = 7$ ), *Polyporus* ( $n = 1$ ), *Pyrofomes* ( $n = 1$ ), and *Trametes* ( $n = 1$ ), described by Guglielmo et al. (14), Robledo et al. (23), Pinruan et al. (20), Yuan et al. (32), and Zhao and Cui (33), were included in the analyses (Table 1). Evolutionary analyses were conducted in MEGA5 (30) with the maximum likelihood method. Evolutionary distances were computed using the Kimura 2-parameter method (16) with 1,000 bootstrap repli-

cates (10). A discrete gamma distribution was used to model evolutionary rate differences among sites.

The complete alignment included 79 sequences. Aligned sequences of the ITS were 866 bp long, including 340 invariable characters, 324 variable parsimony-informative (37.4%) characters, and 108 singletons. Positions containing gaps and missing data were eliminated. The tree comprised 31 described *Perenniporia* species, including the generic type species *P. medulla-panis*. All of the unresolved deeper branches exhibited bootstrap values below 80%, raising concern about the cluster of related species. Furthermore, the tree (outside the ancestral *Abundisporus* branches) included species of *Donkioporia*, *Megasporoporia*, *Polyporus*, *Pyrofomes*, and *Trametes*, which may indicate possible misidentification. The clinical isolate CBS 130020 shared a supported clade (bootstrap, 94%) with unidentified *Agaricomycetes* and a *Megasporoporia* sp. and was found to be identical to the unnamed basidiomycetous endophyte 1V2/2, described by Pinruan et al. (20) (Fig. 3). The nearest taxa are *Perenniporia subacida* and *Perenniporia narymica*, located in a sister clade at a 90% bootstrap level.

Antifungal susceptibility testing (AFST) of the isolate was performed by the CLSI broth microdilution method (5). The antifungals tested were amphotericin B (Sigma, St. Louis, MO), fluconazole (Pfizer, Groton, CT), itraconazole (Lee Pharma, Hyderabad, India), voriconazole (Pfizer), posaconazole (Schering-Plough, Kenilworth, NJ [now Astellas]), isavuconazole (Basilea Pharmaceutica, Basel, Switzerland), flucytosine (Sigma), caspofungin (Merck, Whitehouse Station, NJ), micafungin (Astellas, Toyama, Japan), and anidulafungin (Pfizer). For the broth microdilution

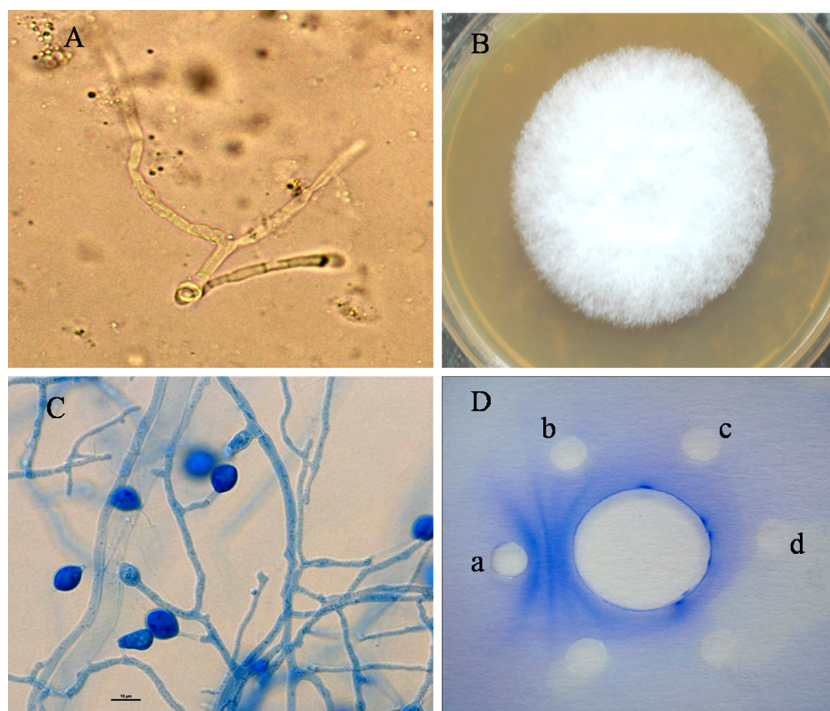


FIG 2 (A) KOH wet mount of BAL fluid specimen of the patient showing hyaline septate hyphae (magnification,  $\times 400$ ). (B) White cottony growth on PDA culture plate seen after 7 days of incubation at 28°C. (C) Slide culture of the isolate on PDA showing hyaline septate hyphae with chlamydoconidia (magnification,  $\times 400$ ). (D) Ouchterlony's agar gel double diffusion test of the patient's serum showing two precipitin bands against a *Perenniporia* species isolate (a) and negative results with antigens of *A. fumigatus* (b), *A. flavus* (c), and *A. terreus* (d).

**TABLE 1** Details of species and internal transcribed spacer (ITS) sequence database accession numbers of reference isolates used in the present study for phylogenetic analysis of *Perenniporia* species (CBS 130020)

Species	Isolate code	Origin	ITS accession no.	Reference
<i>Perenniporiella chaquenia</i>	MUCL 47648	Argentina	FJ411084	23
<i>Perenniporiella chaquenia</i>	MUCL 49758	Argentina	FJ411085	23
<i>Perenniporiella chaquenia</i>	MUCL 47647	Argentina	FJ411083	23
<i>Perenniporiella pendula</i>	MUCL 47129	Cuba	FJ411082	23
<i>Perenniporiella pendula</i>	MUCL 46034	Cuba	FJ411081	23
<i>Perenniporiella micropora</i>	MUCL 43581	Cuba	FJ411086	23
<i>Perenniporiella neofulva</i>	MUCL 45091	Cuba	FJ411080	23
<i>Perenniporia tephropora</i>	Cui 9029	China	HQ876601	33
<i>Perenniporia tephropora</i>	Cui 6331	China	HQ848473	33
<i>Perenniporia maackiae</i>	Cui 8929		HQ654102	33
<i>Perenniporia corticola</i>	Dai 7330		HQ654094	33
<i>Perenniporia corticola</i>	Cui 2655		HQ654093	33
<i>Perenniporia corticola</i>	Cui 1248	China	HQ848472	33
<i>Perenniporia minor</i>	Cui 5738	China	HQ848475	33
<i>Perenniporia minor</i>	Cui 5782	China	HQ883475	33
<i>Perenniporia straminea</i>	Cui 8858		HQ654104	33
<i>Perenniporia straminea</i>	Cui 8718	China	HQ876600	33
<i>Perenniporia ohiensis</i>	Cui 5714		HQ654103	33
<i>Perenniporia ohiensis</i>	MUCL 41036	USA	FJ411096	23
<i>Perenniporia detrita</i>	MUCL 42649	French Guyana	FJ411099	23
<i>Perenniporia ochroleuca</i>	MUCL 39563	Australia	FJ411097	23
<i>Perenniporia ochroleuca</i>	MUCL 39726	Taiwan	FJ411098	23
<i>Perenniporia ochroleuca</i>	Cui 8817	China	HQ848476	33
<i>Perenniporia ochroleuca</i>	Dai 11486		HQ654105	33
<i>Perenniporia nanlingensis</i>	Cui 7620	China	HQ848477	33
<i>Perenniporia nanlingensis</i>	Cui 7541	China	HQ848479	33
<i>Perenniporia minutissima</i>	Dai 11643	China	HQ876602	33
<i>Perenniporia tenuis</i>	Cui 5523	China	HQ848474	33
<i>Perenniporia truncatospora</i>	Dai 5125		HQ654098	33
<i>Perenniporia japonica</i>	Cui 7047		HQ654097	33
<i>Perenniporia rhizomorpha</i>	Cui 7507		HQ654107	33
<i>Perenniporia medulla-panis</i>	Dai 10780		HQ654099	33
<i>Perenniporia medulla-panis</i>	Dai 8736		HQ654100	33
<i>Perenniporia medulla-panis</i>	MUCL 45934	Thailand	FJ411091	23
<i>Perenniporia medulla-panis</i>	MUCL 51629	USA	FJ411090	23
<i>Perenniporia medulla-panis</i>	MUCL 47876	China	FJ411089	23
<i>Perenniporia medulla-panis</i>	MUCL 49581	Poland	FJ411088	23
<i>Perenniporia medulla-panis</i>	MUCL 43250	Norway	FJ411087	23
<i>Megasporoporia setulosa</i>	JV1008_102J	USA	JF894111	Vlasak et al., <sup>a</sup> unpublished data
<i>Megasporoporia setulosa</i>	JV1008_51J	USA	JF894109	Vlasak et al., <sup>a</sup> unpublished data
<i>Megasporoporia setulosa</i>	JV1008_102J	USA	JF894110	Vlasak et al., <sup>a</sup> unpublished data
<i>Perenniporia subadusta</i>	Cui 8459	China	HQ876606	33
<i>Microporellus violaceo-cinerascens</i>	MUCL 45229	Ethiopia	FJ411106	23
<i>Trametes versicolor</i>	M126		HM595570	32
<i>Megasporoporia</i> sp.	Dai 12306		JQ314362	Li et al., <sup>b</sup> unpublished data
<i>Megasporoporia</i> sp.	Dai 12278		JQ314361	Li et al., <sup>b</sup> unpublished data
<i>Perenniporia</i> sp.	E7373	Indonesia	AJ537408	Bougher et al., <sup>c</sup> unpublished data
<i>Perenniporia subacida</i>	Cui 3643		FJ613655	33
<i>Perenniporia subacida</i>	Dai 8224	China	HQ876605	33
<i>Perenniporia subacida</i>	MUCL 31402	Japan	FJ411103	23
<i>Perenniporia narymica</i>	Dai 10510		HQ654101	33
<i>Agaricomycetes</i> sp.	CK		JN630804	Sheikhi et al., <sup>d</sup> unpublished data
<i>Agaricomycetes</i> sp.	India01		HM167516	R. Sasidhara and T. Thirunalasundari, unpublished data
<i>Perenniporia</i> sp.	1V2/2		GQ982890	Pinruan et al., <sup>e</sup> unpublished data
<i>Perenniporia</i> sp.	CBS 130020	India	JX271779	Present study
<i>Megasporoporia</i> sp.	Dai 12170		JQ314363	Li et al., <sup>b</sup> unpublished data
<i>Perenniporia fergusii</i>	Gilbertson 16116	China	HQ876607	33
<i>Polyporus arcularius</i>	CulTENN7883	Costa Rica	AF516524	17
<i>Perenniporia robiniophila</i>	Cui 5644	China	HQ876609	33
<i>Perenniporia robiniophila</i>	Cui 7144	China	HQ876608	33

(Continued on following page)

TABLE 1 (Continued)

Species	Isolate code	Origin	ITS accession no.	Reference
<i>Perenniporia robiniophila</i>	Dai 10416		HQ654096	33
<i>Perenniporia robiniophila</i>	Cui 9174	China	HQ876610	33
<i>Perenniporia vicina</i>	MUCL 44779	Ethiopia	FJ411095	23
<i>Perenniporia fraxinea</i>	Cui 8885	China	HQ876611	33
<i>Perenniporia formosana</i>	Dai 5245	China	HQ876612	33
<i>Perenniporia fraxinea</i>	Cui 7154		HQ654095	33
<i>Perenniporia fraxinea</i>	MUCL 39326	France	FJ411094	23
<i>Perenniporia fraxinea</i>	DP83	Italy	AM269789	14
<i>Pyrofomes demidoffii</i>	MUCL 41034	Russia	FJ411105	23
<i>Donkioporia expansa</i>	MUCL 35116	Belgium	FJ411104	23
<i>Perenniporia martius</i>	MUCL 41677	Argentina	FJ411092	23
<i>Perenniporia martius</i>	MUCL 41678	Argentina	FJ411093	23
<i>Perenniporia martius</i>	Cui 7992	China	HQ876603	33
<i>Perenniporia latissima</i>	Cui 6652	China	HQ876604	33
<i>Abundisporus</i> sp.	MUCL 49566	China	FJ411108	23
<i>Abundisporus violaceus</i>	MUCL 38617	Zimbabwe	FJ411100	23
<i>Abundisporus sclerosetosus</i>	MUCL 41438	Singapore	FJ411101	23
<i>Abundisporus roseoalbus</i>	MUCL 49583	China	FJ411102	23
<i>Abundisporus roseoalbus</i>	MUCL 49622	China	FJ411107	23

<sup>a</sup> J. Vlasak, J. Kout, Jr., J. Vlasak, and L. Ryvarden.

<sup>b</sup> H. J. Li, B. K. Cui, and Y. C. Dai.

<sup>c</sup> N. L. Bougher, I. C. Tommerup, S. R. H. Langrell, S. Q. Bolsenbroek, and J. M. Catchpole.

<sup>d</sup> F. Sheikhi, M. Roayaei Ardakani, and N. Enayatizamir.

<sup>e</sup> U. Pinruan, N. Rungjindamai, R. Choeyklin, S. Lumyong, and G. Jones.

test, RPMI 1640 medium with glutamine without bicarbonate (Sigma) buffered to pH 7 with 0.165 mol/liter 3-*N*-morpholinepropanesulfonic acid (Sigma) was used. Isolates were grown on PDA for 8 days at 37°C, and the inoculum was adjusted to a final density of  $1.0 \times 10^4$  to  $5.0 \times 10^4$  hyphal fragments/ml measured by a spectrophotometer. Drug-free and mold-free controls were included, and microtiter plates were incubated at 35°C for 72 h. CLSI-recommended quality control strains *Candida krusei* ATCC 6258 and *Candida parapsilosis* ATCC 22019 and reference strains *Aspergillus fumigatus* ATCC 204305 and *Aspergillus flavus* ATCC 204304 were included. The MIC endpoints were read visually; for azoles and amphotericin B, MICs were defined as the lowest concentration at which there was 100% inhibition of growth compared with the drug-free control wells. For echinocandins, minimal effective concentrations (MECs) were defined as the lowest concentration of drug that led to the growth of small, rounded, and compact hyphal forms. For the isolate, the lowest MIC was that of posaconazole (0.06 µg/ml), followed by itraconazole (0.5 µg/ml), voriconazole (2 µg/ml), and isavuconazole (2 µg/ml). Amphotericin B had a MIC of 0.25 µg/ml. All three echinocandins showed good activity (MECs, 0.125 to 0.5 µg/ml). Fluconazole and flucytosine did not show any activity (64 µg/ml).

The clinical significance of white, cottony, rapidly growing filamentous molds from pulmonary samples is poorly understood. In the past, cultures have often been discarded as purported contaminants, because morphological identification of these nonsporulating fungi was impossible, and hence, they could not be attributed to any of the known pathogens. Today, we know that many of these cultures are of basidiomycete affinity (9). The most common of these is *Schizophyllum commune*, which is recognizable morphologically by the presence of hyphal pegs (26) and sometimes by

clamp connections and by the formation of abortive fruiting bodies (3). Occasionally, another basidiomycete repeatedly isolated from pulmonary infections in humans is *Hormographiella aspergillata*, the anamorph of the Agaricales mushroom *Coprinopsis cinereus* (11, 13, 27, 28, 31). The *Coprinopsis* species are recognizable in culture by the formation of arthroconidial anamorphs (9). Recently, some lesser-known basidiomycete species, such as *Cyclomyces tabacinus* (18), *Irpex lacteus* (2), *Inonotus (Phellinus) tropicalis* (7, 29), *Oxyporus corticola* (1), and *Volvariella volvacea* (25), have been added as causative agents of pulmonary and fatal deep-seated mycoses in humans and animals. Other basidiomycetes such as *Phanerochaete chrysosporium* (anamorph, *Sporotrichum pruinosum*) and *Bjerkandera adusta* have repeatedly been isolated from pulmonary sites and may also be pathogenic in some settings (12, 15).

The majority of infections caused by filamentous basidiomycetes are associated with chronic colonization of cavities in lungs or sinuses (3, 21, 26). Occasionally, however, this may lead to fatal dissemination and cerebral involvement, implying that this fungal group may have a neurotropic potential (22). As long as there is a paucity of information on fungus and host responses for filamentous basidiomycetes, infections by these fungi should be treated with caution. The present case demonstrates a novel agent of fungal ball due to a *Perenniporia* species. The case was diagnosed by CECT showing intracavitary mass, by bronchoscopy, by direct demonstration (KOH wet mount), and by isolation of the species in culture from BAL fluid. Serological analysis demonstrated precipitins against the etiologic agent. Many patients with fungal ball are asymptomatic, but the most frequent symptom is hemoptysis. Less commonly, patients develop chest pain, dyspnea, malaise, and wheezing. In the present case, the patient was afebrile with a history of mild hemoptysis. In asymptomatic patients, no treatment is required, regular observation being sufficient in most

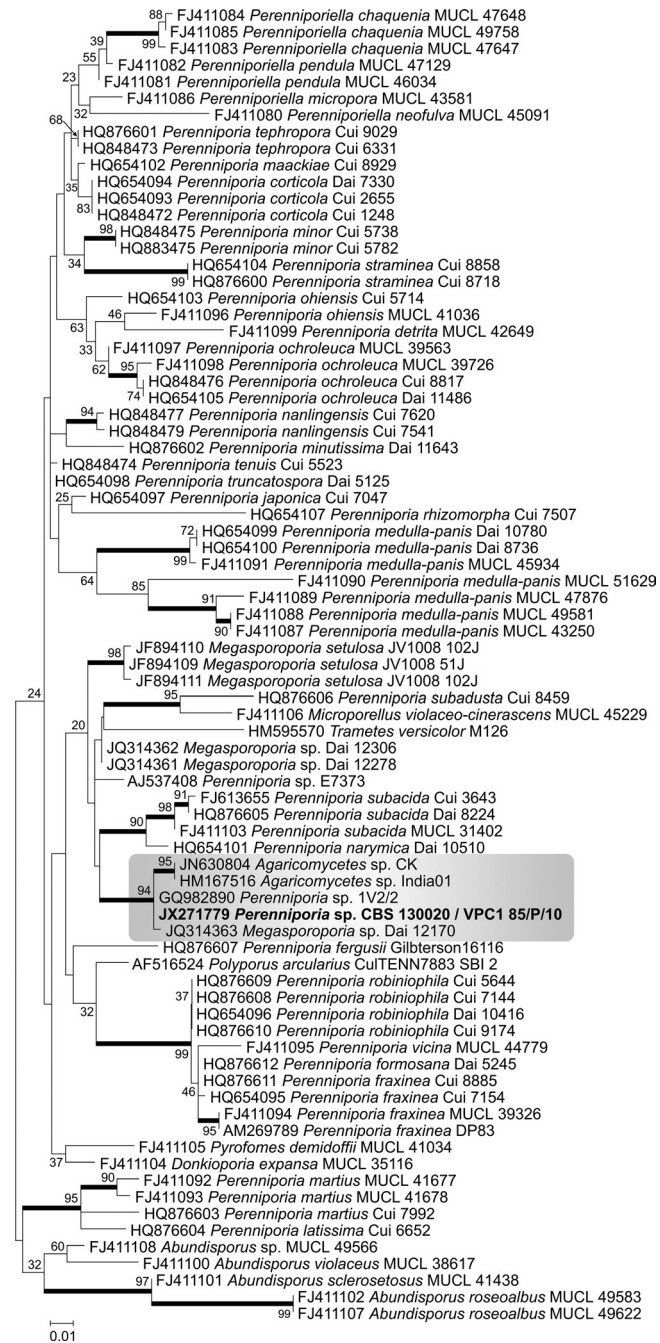


FIG 3 Molecular phylogenetic tree based on ITS sequences generated in this study by the maximum likelihood method based on the Kimura 2-parameter model. The percentage of replicate trees in which the associated taxa clustered together in the bootstrap test (1,000 replicates) is shown next to the branches (bootstrap support values of >90% are indicated in bold). GenBank accession numbers are indicated before the strain code.

cases. There is no consistent evidence that fungal ball responds to antifungal agents, and such drugs rarely achieve the effective concentrations within the lung cavities (19).

The isolate did not show the characteristics that facilitated recognition of a filamentous basidiomycete such as the presence of clamp connections and/or crystals, the formation of spicules along the hyphae, and mushroom- or basidiocarp-type fruiting

bodies. Since most clinical isolates are monokaryons, neither clamps nor fruiting structures are produced. The isolate was proven to be affiliated with the filamentous basidiomycetes through sequencing. Definite identification was impossible, because it showed 100% identity with an as-yet-unidentified species attributed to *Perenniporia* and it was close to several unnamed basidiomycete species (Fig. 3). The nearest named species was *Megasporoporia setulosa*, at a 10% ITS distance. Taxonomically, *Perenniporia* and *Megasporoporia* belong to the order Poriales in the Agaricomycetes, Basidiomycota. Fungi of this group are characterized morphologically by formation of porate, often resupinate fruiting bodies which are flat on the substrate with the hymenium on the outer side on rotten branches. The genus *Perenniporia* contains numerous species growing as saprobes on dead wood (6, 33). They are ubiquitously present under almost all types of climatic conditions, degrading wood by decomposition of lignin and, to a limited extent, cellulose, leading to white rot. Most species are presently known from herbarium materials only and have not been sequenced. The fact that the sequence of our strain did not have a match in GenBank is therefore not surprising, as there are not enough data in GenBank to identify unknown sterile basidiomycetes with a high degree of confidence by ITS and/or D1/D2 sequencing (24). Through GenBank, similarities also were found with other genera of shelf fungi, such as *Trametes*, *Donkioporia*, and *Pyrofolium* (Fig. 3). The taxonomy of these fungi has insufficiently been resolved using modern, nonmorphological techniques, and the sequences available thus far do not clearly resolve the genera (Fig. 3). Therefore, description of our strain as a novel species in any of the genera mentioned does not seem to be appropriate. In our tree (Fig. 3), the name *Perenniporia* is widely distributed (31 described species). The generic type species, *P. medulla-panis*, included in the tree is represented by strains studied by Decock and Stalpers, who rectified the generic typification (8). This and several other *Perenniporia* species show variability in the sequenced gene. *Perenniporia medulla-panis* occupies a central location compared to the remaining species, and the main branches lack statistical support, indicating concerns due to related taxa. Therefore, attribution of our strain to the genus *Perenniporia* is justified.

*Perenniporia* species have never been reported as etiologic agents of human disease before. Similarly to *Schizophyllum*, the fungus produces large amounts of airborne basidiospores which are easily inhaled. The frequency with which this leads to colonization of pulmonary cavities or systemic dissemination is presently unknown. This report extends the genera of basidiomycetous fungi implicated in pulmonary infections and underscores the utility of molecular methods in the identification or verification of these often unidentifiable molds when conventional mycological techniques fail to identify the incriminated fungi (21).

**Nucleotide sequence accession numbers.** The ITS and LSU nucleotide sequences for the isolate CBS 130020 were deposited in GenBank under the accession numbers JX271779 and JX292098, respectively.

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