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Scopulariopsis, a Poorly Known Opportunistic Fungus: Spectrum of Species in Clinical Samples and In Vitro Responses to Antifungal Drugs

Marcelo Sandoval-Denis, Deanna A. Sutton, Annette W. Fothergill, Josep Cano-Lira, Josepa Gené, C. A. Decock, G. S. de Hoog, Josep Guarro

The genus Scopulariopsis contains both hyaline and dematiaceous molds, and their teleomorphs are included in the genus Microascus (order Microascales). They are saprobes commonly isolated from soil, air, plant debris, paper, and moist indoor environments (1–3). Some species are known to be opportunistic pathogens, mainly causing superficial tissue infections, and they represent some of the principal causes of nondermatophytic onychomycoses (4, 5). Less common clinical manifestations include keratitis following eye trauma (6) and otomycosis (7). The fungi have also been involved in deep tissue infections, mainly in immunocompromised and occasionally in immunocompetent patients, causing, for example, pneumonia (8), endophthalmitis (9), subcutaneous and brain abscesses (10, 11), invasive sinusitis (12), peritonitis (13), and endocarditis (14, 15). The most frequently reported species in all clinical presentations and anatomic sites in deep tissue infections is Scopulariopsis brevicaulis. Other less frequent species are Scopulariopsis aereocronium, Scopulariopsis brumptii, Scopulariopsis flava, Microascus nigер, Microascus cinereus, Microascus cirrosus, Microascus manginii, and Microascus trigonosporus (5, 16–18).

Currently, there are close to 40 accepted species of Scopulariopsis and Microascus. For many of these species, the anamorph-teleomorph connection has already been established (1, 5, 16). However, the sexual states of some Scopulariopsis species are still unknown.

According to the new International Code of Nomenclature for fungi, algae, and plants, the dual nomenclature system that has been traditionally used for fungi, which includes both anamorph and telemorph states, is no longer allowed and hence a unique name must be chosen (19). We judge that since the name Scopulariopsis has been used much more frequently in the literature, including in medical publications, this name should have priority over Microascus. However, since no formal proposal has yet been submitted, in the present paper we apply the traditional nomenclature for known Scopulariopsis and Microascus species.

Although the isolation of Scopulariopsis species from clinical specimens is relatively easy, as they grow well on routine laboratory media, it might be difficult to identify them morphologically down to the species level (18). Histopathology has limited significance in diagnostics since in tissue, the fungi show features similar to those of other more common pathogenic molds, such as Aspergillus or Fusarium species (18, 20). The sequencing of the ribosomal operon has been used for the identification of clinical strains of Scopulariopsis, although the results may not be reliable because of insufficient availability of reference sequences in the public databases (17, 18, 21, 22). Interestingly, due to the high genetic variability of the internal transcribed spacer (ITS) sequences found in a large set of Scopulariopsis strains isolated from cheese, Ropars et al. (23) used the combined analysis of partial sequences of the long subunit (LSU) rRNA gene, β-tubulin (TUB), and elongation factor 1-α (EF1-α) genes for the taxonomic circumscription of Scopulariopsis species and proposed the EF1-α gene to be the most phylogenetically informative genomic region for identifying Scopulariopsis species.

The high rates of resistance of these fungi to practically all currently used antifungal agents, including amphotericin B (AMB) and voriconazole (VRC), which are among the most commonly used drugs for the prophylaxis and first-line treatment of systemic mold infections, is significant. The appropriate therapy for Scopulariopsis infections has yet to be defined (22, 24). The effectiveness of AMB has been estimated to be only about 40% of successful treatments (24), which has resulted in high mortality...
rates and infection relapses (15, 20). In vitro antifungal susceptibility studies on these fungi are scarce and have involved mainly topical drugs. Several clinical reports have underlined the lack of correlation between in vitro susceptibility test results and clinical outcomes (21, 22, 25).

Because in most of the clinical reports of Scopulariopsis infections, morphological identification of the etiological agent has not been confirmed at the molecular level, the real prevalence of Scopulariopsis species in clinical samples, apart from those from S. brevicatulís, is unknown. We therefore studied a large set of clinical isolates, most of which were received at a mycology reference laboratory in the United States, in order to define the species spectrum and the relative frequencies of Scopulariopsis in clinical specimens. The in vitro antifungal susceptibilities of the most prevalent species were also determined.

**MATERIALS AND METHODS**

**Fungal isolates and sequences.** Ninety-nine clinical isolates received as *Scopulariopsis* or *Microascus* species were included in this study. In addition, 23 type and reference strains were studied. Five D1/D2 rRNA gene and six elongation factor 1-α gene (EF1-α) sequences retrieved from GenBank were also included in the phylogenetic analyses.

**Morphological identification.** The isolates were subcultured onto potato-dextrose agar (PDA) (Pronadisa, Spain), oatmeal agar (OA) (30 g of filtered oat flakes, 20 g of agar, 1 liter of distilled water), and potato–carrot agar (PCA) (20 g each of filtered potatoes and carrots, 20 g of agar, 1 liter of distilled water) up to 21 days at 25°C in darkness. The microscopic features were obtained from direct wet mounts and slide cultures on PDA, OA, or PCA, mounted in lactic acid or lactophenol. All isolates were morphologically identified as per Morton and Smith (2), de Hoog et al. (5), and Guarro et al. (26).

**DNA extraction, amplification, and sequencing.** Isolates were grown on YES agar (20 g of yeast extract, 150 g of sucrose, 20 g of agar, 1 liter of distilled water) for 5 days at 25°C. The total genomic DNA was extracted from agar cultures using the PrepMan Ultra sample preparation reagent (Applied Biosystems, Foster City, CA), according to the manufacturer’s protocol. DNA was quantified using a Nanodrop 3000 (Thermo Scientific, Madrid, Spain).

To amplify a 440-bp fragment of the D1/D2 domains of the 28S rRNA gene and a 1,200-bp fragment of the EF1-α gene, we used the primers and protocols described previously by O’Donnell (27) and Rehner and Buckley (28), respectively. The amplified products were purified with the DImity RapidTip purification system (Sigma-Aldrich, St. Louis, MO, USA) and stored at −20°C until sequencing.

Sequencing was made in both directions with the same primer pair used for amplification at Macrogen Europe (Macrogen Inc., Amsterdam, The Netherlands). The consensus sequences were obtained using the SeqMan software version 7.0.0 (DNASTar Lasergene, Madison, WI, USA).

**Molecular identification and phylogenetic analysis.** Preliminary molecular identification of the isolates was performed using BLAST searches for both amplified fragments. Only the sequences of type or reference strains deposited in the GenBank/EMBL database were considered for identification purposes. A maximal level of identity (MLI) of ≥98% was considered to allow for a species-level identification. MLI values of <98% provided identification only at genus level.

Multiple sequence alignments were made in MEGA version 5.05 (29) using the ClustalW application (30) and manually refined under the same software platform. The ambiguous areas of the alignment were removed using the Gblocks server (http://molevol.cmima.csic.es/ castresana/Gblocks_server.html) (31).

**Results**

Of the 99 isolates studied, 97 were morphologically identified as members of the *Scopulariopsis* or *Microascus* genus. The remaining two isolates were identified as a *Scedosporium* sp. and *Phialosimplex caninus*, respectively. The *Scopulariopsis* isolates were characterized by moderately fast growth and flat, velvety or powdery, white, tan, dark brown, gray, or black colonies. Microscopically, they showed hyaline or dematiaceous septate hyphae with cylindrical or flask-shaped conidiogenous cells (anellides) formed singly or in small groups directly on the vegetative hyphae or on short and usually branched conidiophores. The conidia were one celled, hyaline, light green to dark brown, flat at the base, globose, limoniform or bullet-shaped with a smooth or rough surface, hydrophobic, and produced in long chains. When present, teleomorphs were characterized by dark, ostiolate, globose to pyriform perithelia with or without a neck, superficial or immersed in the agar. The asci were ovate and evanescent and contained eight one-celled, straw-colored, asymmetrical, reniform, lunate, or triangular ascospores.

**Figure 1** shows the phylogenetic tree inferred from the ML and Bayesian analyses of the concatenated EF1-α and D1/D2 sequences of a representative number of the clinical isolates tested in this study, including the type and reference strains of clinically relevant species of the genus. Of the 48 isolates identified as *S. brevicatulís*, 8 were randomly chosen for the phylogenetic analysis, since the isolates in this group showed a high sequence similarity (>99.3%). In the tree, the clades are named according to the degree of similarity with the type or reference strains of known species. Twenty-three well-supported clades were formed, 14 of which corresponded with previously recognized species. The *S. gracilís* clade grouped the type strain of this species together with 14 clinical isolates. All the isolates were characterized by the production of abundant conidia, usually from well-differentiated branched conidiophores. Ten of these isolates also developed ascomata and ascospores morphologically very similar to those of *M. cinereus*. However, they can be distinguished from *M. cinereus* mainly by having lunate ascospores, measuring 4.5 to 6.5 by 2 to 4 μm, and by the presence of branched conidiophores
The isolates belonging to the clade of *M. cinereus sensu stricto* showed ascospores of variable shape (reniform, broadly lunate, or triangular) and that were slightly smaller (4 to 5.5 by 2.5 to 4 μm), and the conidiophores were mostly simple, usually reduced to a single conidiogenous cell growing directly on the vegetative hyphae (Fig. 2).

Ten isolates that morphologically resembled *M. trigonosporus* were grouped in the clades *Scopulariopsis* sp. I, II, and VI, which

**FIG 1** Maximum likelihood tree obtained from the combined EF1-α and D1/D2 sequences of representative isolates. In the tree, the branch lengths are proportional to phylogenetic distance. Bootstrap support values of ≥70/Bayesian posterior probability scores of ≥0.95 are indicated on the nodes. The supported branches and type strains are shown in bold type. *T*, type strain.
were phylogenetically distant from the type strain of that species (CBS 218.31), i.e., they have 97.8%, 97.6%, and 98.0% sequence similarities, respectively.

The clades 

Scopulariopsis sp. III to V, VII, and VIII comprise 6 clinical isolates that were not morphologically similar or phylogenetically related to any known species.

A large clade, named the 

S. candida complex, includes the etype of 

S. candida, a reference strain of 

M. manginii, three reference strains of 

M. niger, and three clinical isolates, two of which had been morphologically identified as 

S. candida and one as 

M. niger. Since the different species included in this group showed high sequence similarities (>98.7%) but exhibited different morphological characteristics, all the species included in this group were treated as a complex. The two clinical isolates grouped in the clade 

Scopulariopsis sp. IX were morphologically identified as 

M. manginii but proved to be phylogenetically distant from the reference strain of this species (MUCL 41467) and from the epitype of its anamorph 

S. candida (<97.9% and <98.2% sequence similarities, respectively).

Molecular identification showed that the most common species was 

S. brevicaulis (49.4%) followed by 

S. gracilis (14.4%), S. brumptii (7.2%), 

M. cinereus (5.2%), the 

S. candida species complex (3.1%), and 

M. cirrosus (2.1%). Table 1 summarizes the key morphological features for distinguishing the most common species identified in this study. The correlation between morphological and molecular identifications at the species level was 67%. The remaining isolates were identified with confidence only at the genus level.

Most clinical isolates studied were of respiratory origin (61.6%), mainly obtained from bronchoalveolar lavage (BAL) fluid and sputum samples, followed by superficial tissue samples (19.2%) principally isolated from the nails and skin. The remaining 19.2% of isolates were from miscellaneous deep tissue or sterile fluid specimens (Table 2). 

S. brevicaulis was the most common species from all clinical origins. 

S. gracilis was most frequently isolated from BAL fluid and sputum samples, while 

S. brumptii and 

M. cirrosus were only recovered from lower respiratory tract samples.

The results of the antifungal susceptibility testing are summarized in Table 3. All antifungal drugs showed similar low activities. AMB showed an overall geometric mean MIC (GM) and MIC90 of 16.9 μg/ml and 32.0 μg/ml, respectively. The activities of the azoles were similar for all the species tested; VRC and PSC displayed GM values of 16.4 μg/ml and 14.6 μg/ml, respectively. In contrast, ITC showed almost no activity, with an MIC90 of ≥32 μg/ml. The echinocandins had the highest activities, with overall GMs of 4.0 μg/ml, 3.7 μg/ml, and 1.1 μg/ml for anidulafungin (AFG), caspofungin (CFG), and micafungin (MFG), respectively. TRB also showed limited activity, with an overall GM and MIC90 of 1.9 μg/ml and 8 μg/ml, respectively. 

M. cinereus and the 

S. candida complex were the most susceptible species.

DISCUSSION

This study involved the highest number of isolates of 

Scopulariopsis and 

Microascus of clinical origin ever to be evaluated to date. In agreement with earlier reviews of clinical cases (17, 22), 

S. brevicaulis was the most commonly isolated species in our study. 

S. gracilis was the second most commonly isolated species in our study, which is interesting since this fungus has never been reported in human infections or isolated from clinical specimens. In numerous isolates of this species, a sexual state was present that morphologically resembled that of 

M. cinereus. The teleomorph of 

S. gracilis probably has never been described in the literature because it is often confused with 

M. cinereus. In a recent review of 33 human invasive infections from 

Scopulariopsis or 

Microascus species, 

M. cinereus was, after 

S. brevicaulis, the second most commonly isolated species (12%) (17). However, our study emphasized some difficulties in the morphological identification of this species, since almost a third of the isolates morphologically identified as 

M. cinereus were found after sequencing to be from 

S. gracilis. The inadequacy of the morphological criteria was also
TABLE 1 Key morphological features of the most commonly identified species in this study

| Species                               | Colony color | Ascomata | Conidiophores | Conidia | Shape | Total no. (%) of \n|----------------------------|--------------|---------|---------------|---------|-------|-----------------|
| Microascus cirrosus                  | Yellowish-brown | 4–5.5 by 3.5–4.5 | Smooth | Bottleshaped | 4–5.5 by 3–5 | Broadly reniform | 0 0 0 2 2 (2.1) |
| Microascus niger                     | Greenish-gray | 4–5.5 by 2.5–4 | Bottle-shaped | Single or in groups (2–5) | 4–5.5 by 2–4 | Obovate | 19 (19.2) |
| Microascus manginii                  | Brownish-gray | 3–5 by 2–3 | Smooth | Single or in groups (2–5) | 3–5 by 2–3 | Obovate | 0 0 0 7 7 (7.2) |
| Scopulariopsis candida               | Black        | 4.5–6 by 2–4 | Bottle-shaped | Single or in groups (3–10) | 4.5–6 by 2–4 | Obovate | 0 0 0 2 2 (2.1) |
| Scopulariopsis gracilis              | Greenish-brown | 4–6 by 2.5–4.5 | Smooth or clavate | Lunate | 4.5–6.5 by 2–4 | Bottle-shaped | 11 (11.1) |
| Scopulariopsis brasiliensis          | Light brown | 3.5–5 by 2–3.5 | Verrucose | Globose or ovoid | 5–7 by 5–7 | Verrucose | 15 (15) |
| Scopulariopsis brevicaulis           | Olive gray | Present or absent | Well-differentiated branched conidiophores usually on well-differentiated branched conidiophores | Present | 5–8 by 5–7 | Verrucose | 8 (8) |
| Scopulariopsis brumptii              | Yellowish-brown | 3.5–5.5 by 2–3.5 | Smooth | Bottle-shaped | 4–5.5 by 2–4 | Obovate | 0 0 0 1 1 (1.1) |

TABLE 2 Anatomical sources of clinical isolates of Scopulariopsis and Microascus spp.

<table>
<thead>
<tr>
<th>Species</th>
<th>No. of isolates obtained from</th>
<th>Surgical fluids</th>
<th>Upper respiratory tract</th>
<th>Lower respiratory tract</th>
<th>Deep tissue</th>
<th>Total nos. of isolates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scopulariopsis candida</td>
<td>15 (15)</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>10 (10)</td>
<td>2 (2)</td>
<td>30 (30)</td>
</tr>
<tr>
<td>Scopulariopsis gracilis</td>
<td>10 (10)</td>
<td>3 (3)</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>18 (18)</td>
</tr>
<tr>
<td>Scopulariopsis brumptii</td>
<td>8 (8)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>3 (3)</td>
<td>1 (1)</td>
<td>9 (9)</td>
</tr>
</tbody>
</table>
Interestingly, most *S. gracilis* and *M. cinereus* and all *S. brumptii* and *M. cirrosus* isolates tested in our study were from respiratory samples, which suggests a tendency toward localization at this anatomic site. Considering that most of the isolates from a respiratory origin (68%) have been obtained from BAL fluid samples rather than from proven cases, the possible role of these fungi in lung infection warrants further research.

With the exception of the study by Aguilar et al. (24), the antifungal susceptibilities of *Scopulariopsis* and *Microascus* species have been evaluated mainly in *S. brevicaulis* (25, 37–39). Although our study included newer antifungals, the results generally agree with previous data, showing resistance to practically all the available antifungal drugs. Similar data were obtained with testing of other fungi also belonging to the *Microascales*, such as *Scedosporium* spp. (40). In our study, susceptibility to AMB was rarely observed, VRC and PSC showed moderate activities against only a few isolates, and ITC and TBF showed almost no activity. The echinocandins, especially MFG and AFG, demonstrated better *in vitro* activities than the azoles; however, a high number of resistant isolates were also detected. Since no treatment guidelines are available for this group of fungi, therapies for most reported clinical cases were based on previous experience with those used for *Aspergillus* or other clinically relevant molds. Although most clinical cases reported negative outcomes regardless of the type of antifungal treatment (20, 22), VRC has shown some clinical efficacy (11, 15). Our results showed similar *in vitro* activities for VRC and PSC, although there are no clinical reports using PSC. Echinocandins have only rarely been used to treat *Scopulariopsis* infections. Beltrame et al. (41) unsuccessfully used CFG after negative results with VRC in a case of fungal sinusitis caused by *S. acremonium*. More recently, Iwen et al. (17) reported a negative outcome with a combination of liposomal AMB plus MFG against an invasive infection by *S. brevicaulis*.

In conclusion, although infrequent, systemic *Scopulariopsis* and *Microascus* infections are difficult to treat and hence are frequently fatal. Morphological species-level identification is difficult; the combined analysis of EF1-α and D1/D2 can be useful for the identification of the most common clinically relevant species. The isolates studied here showed high levels of resistance to the currently available antifungal agents.

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### REFERENCES


### TABLE 3 Results of *in vitro* antifungal susceptibility testing of *Scopulariopsis* and *Microascus* species

<table>
<thead>
<tr>
<th>Data by species (no. of isolates tested)</th>
<th>MIC/MEC parametera</th>
<th>AMB</th>
<th>VRC</th>
<th>ITC</th>
<th>PSC</th>
<th>AFG</th>
<th>CFG</th>
<th>MFG</th>
<th>TRB</th>
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<td>19.0</td>
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<td>1–32</td>
<td>1–32</td>
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<td>1–16</td>
<td>0.06–16</td>
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<td>32</td>
<td>32</td>
<td>32</td>
<td>16</td>
<td>16</td>
<td>16</td>
<td>2</td>
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<td>GM</td>
<td>19.5</td>
<td>26.3</td>
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<td>20.5</td>
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<td>7</td>
<td>32</td>
<td>4</td>
<td>8</td>
<td>1</td>
<td>2</td>
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<td><em>Microascus cinereus</em> (5)</td>
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<td>16</td>
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<td>4</td>
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<tr>
<td><em>Scopulariopsis candida</em> complex (3)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>GM</td>
<td>3.2</td>
<td>32.0</td>
<td>32.0</td>
<td>32.0</td>
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<tr>
<td><em>Microascus cirrosus</em> (2)</td>
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<td>32.0</td>
<td>5.7</td>
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<td>16</td>
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</table>

<sup>a</sup> GM, geometric mean; MIC<sub>50</sub>, drug concentration that inhibited 90% of isolates, shown only for groups with ≥5 isolates.

<sup>b</sup> AMB, amphotericin B; VRC, voriconazole; ITC, itraconazole; PSC, posaconazole; AFG, anidulafungin; CFG, caspofungin; MFG, micafungin; TRB, terbinafine.

<sup>c</sup> Includes *Scopulariopsis asperula*, *Scopulariopsis candida*, *Scopulariopsis fusca*, *Microascus manginii*, and *Microascus niger*. 

*ănglynn*
Scopulariopsis in Clinical Samples


