

1 **Successful terbinafine treatment of cutaneous phaeohyphomycosis caused by**

2 ***Trematosphaeria grisea* in a heart transplanted man: case report and literature review**

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21 **Short running title:** Overview of terbinafine usage during phaeohyphomycosis and case report involving *T.*

22 *grisea*

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28 **Abstract**

29 Phaeohyphomycosis is chronic infectious disease caused by dematiaceous fungi. It is characterized by the
30 presence of pigmented septate mycelia within tissues. In case of superficial infection, the lesion(s) chronically
31 evolve towards painless pseudo-tumors of the soft parts. We report herein the original case of a heart
32 transplanted man who exhibited phaeohyphomycosis of the left hand, with no mention of travels in endemic
33 areas. *Trematosphaeria grisea* was identified as the causative agent, which is quite innovative since this species
34 has been rather described in mycetoma. The antifungal treatment initially based on isavuconazole alone was not
35 sufficient to cure the patient. In contrast, its association with local terbinafine ointment allowed total clinical
36 improvement. This finding is unusual as diagnosis of phaeohyphomycosis caused by *T. grisea* is uncommon in
37 non-tropical countries, and as the outcome appeared successful by the means of add-on therapeutic strategy with
38 terbinafine.

39

40 Keywords: phaeohyphomycosis – dematiaceous fungus – *Trematosphaeria grisea* – isavuconazole – terbinafine

41

42 **Introduction**

43 Dematiaceous fungi are ubiquitous molds colored in pale brown-to-black due to the presence of melanin within
44 their cell wall. They can cause chromoblastomycosis, mycetoma or phaeohyphomycosis. Phaeohyphomycosis
45 refers to as a group of infections characterized by the presence of pigmented septate mycelia - but neither grains
46 (that are pathognomonic to mycetoma) nor Medlar sclerotic cells (pathognomonic to chromoblastomycosis) -
47 within tissues [1]. It is potentially caused by a great variety of fungal genera [2]. Phaeohyphomycosis has been
48 mostly reported in tropical areas, both in immunocompromised and non-immunocompromised hosts [3,4].
49 Clinical signs vary largely. Therefore, phaeohyphomycosis is nowadays usually classified in three distinct
50 subtypes: local superficial infection, local deep infection or disseminated infection. In case of local superficial
51 infections, phaeohyphomycosis is generally due to the inoculation of the causative agent directly into the skin
52 following trauma; then, the fungus and the surrounding inflammation grow over several years to result in a
53 painless pseudo-tumorous mass. Laboratory tests allow the species identification by the means of *in vitro* culture
54 and molecular sequencing, but there is no diagnostic assay available for blood. The therapeutic management is
55 challenging. We present herein an original case of phaeohyphomycosis in a heart transplanted man caused by
56 *Trematosphaeria grisea* (syn. *Madurella grisea*), that is a fungal species usually rather involved in mycetoma
57 [6]. Curative treatment with terbinafine was successful.

58

59 **Observation**

60 A 49-year-old man was referred for a painless tumorous lesion located at the left hand. It was significantly
61 expanding over a one-month period. The patient had never left France, except for a short stay in Tunisia, ten
62 years before. He also reported the inoculation of a foreign body into his left hand, following a road accident in
63 metropolitan France few years ago. Three months before the present consultation, he underwent cardiac
64 transplantation because of heart failure. He was currently given an immunosuppressive treatment based on
65 mycophenolate mofetil, prednisone and tacrolimus monohydrate. At the physical examination, a bluish four
66 centimeter-long abscessed and suppurated lesion of the soft parts was noticed on the dorsal side of the hand. The
67 lesion was facing the third and fourth **Erreur ! Source du renvoi introuvable.** extensor muscle's tendon (Figure
68 1a, Figure 2). There was neither paresthesia nor sensory-motor deficiency. No satellite adenopathy was reported.

69 The abscess was drained (but the pus was not investigated), and a biopsy of the lesion was concomitantly
70 performed. Histological examination showed pigmented mycelial structures without grains (Figure 3). The
71 macroscopic features of colonies that were isolated *in vitro* first suggested *Madurella* genus (Figure 4).
72 Eventually, the species *Trematosphaeria grisea* (syn. *Madurella grisea*) was confirmed by DNA sequencing
73 through genomic amplification of the rDNA 28S D1-D2 region (Score GenBank = 1133; cover= 99%;
74 identit.=100%; GenBank accession number MN581332). The absence of fructification and sporulation did not
75 allow measurement of the antifungal MICs (minimum inhibitory concentrations). For the initial curative
76 treatment, isavuconazole, at the conventional dosage of 200 mg *qd* (after an initial loading dose over 48h), was
77 empirically chosen due to its theoretical efficiency against *Madurella* species and its drug-to-drug interactions
78 that are assumed quite limited with immunosuppressive drugs [7]. Furthermore, isavuconazole does not require
79 dosage adaptation in case of kidney insufficiency, the patient having herein a glomerular filtration rate at 47
80 mL/min. No clear clinical improvement was noticed over the next nine months; so, daily application of topic
81 terbinafine ointment was added to oral isavuconazole. Two months later, substantial reduction of the lesion size
82 was noticed (Figure 1b), so that the antifungal combination strategy was pursued for six additional months.
83 Afterwards, side effects occurred with diarrhea, and the renal function decreased due to possible interaction of
84 the oral antifungal with tacrolimus monohydrate. The therapeutic drug monitoring showed high residual
85 concentrations of isavuconazole (5.20 mg /L in blood). Isavuconazole was then withdrawn, and instead oral
86 therapy with terbinafine alone was initiated with a dosage at 250mg *per* day. The total excision was denied by
87 the patient. After six months of terbinafine alone, the lesion almost disappeared (Figure 1c), while the tolerance
88 was satisfactory, so that the dosage was reduced at 250 mg every other day. After one year of treatment with oral
89 terbinafine, the lesion is no more visible.

90

91 **Discussion**

92 Burgeoning and invasive masses of the soft parts can evoke a skin tumour, like cutaneous carcinoma [8].
93 Phaeohyphomycosis - and more largely fungal infection of the skin and subcutaneous tissues - is often
94 overlooked, because not well known by most of the practitioners. As there are no rapid and reliable serologic or
95 immunologic tests that can be easily implemented for diagnosis of phaeohyphomycosis, biopsies with
96 mycological and histological investigations must be systematically performed in case of any doubt.

97 Nowadays, the number of pathogenic fungi documented as causative agents of phaeohyphomycosis has reached
98 70 genera and 150 species [9]. The recent application of molecular and phylogenetic tools has largely revised the
99 taxonomic placement of melanised mycetes. Using a multigene phylogenetic approach, Ahmed *et al.* concluded
100 that *Trematosphaeria grisea* species (syn. *Madurella grisea*) is phylogenetically-affiliated to the
101 Trematosphaeriaceae family, suborder Massarineae in the Pleosporales order [6]. Although not so common, *T.*
102 *grisea* has long been acknowledged as an exclusive agent of mycetoma in South America, more precisely in
103 Brazil [10,11] and in Chile (but also in a submandibular abscess in India [6]). However, demonstration of its
104 involvement in phaeohyphomycosis is more recent, maybe because there was previously a lack of correct
105 identification [12]. Morphologically, *T. grisea* colonies are usually described as rugose-cottony-brown of slow
106 growth rate at 30° C. A brownish pigment diffuses into the agar. Microscopic examination reveals long septate
107 hyphal elements with chains of arthroconidia. However, further analysis with yeast nitrogen base shows that *T.*
108 *grisea* assimilates glucose, maltose and saccharose, but not lactose [11], whereas *M. mycetomatis* is able to
109 assimilate glucose, maltose and lactose, but not saccharose [13]. Nowadays, modern tools available such as mass
110 spectrometry or DNA sequencing can identify whole unusual kinds of microorganisms from the subculture, as
111 long as the references for fragmentation mass patterns or DNA sequences exist in the data bank. So herein, we
112 are able to distinguish between *T. grisea* and *Madurella mycetomatis*, *i.e.* the major species of the *Madurella*
113 genus which is usually more frequently involved in mycetoma.

114 The present case report is original since the patient did not come from endemic tropical area and had been
115 always living in France, except for a unique travel in Tunisia ten years before the heart transplantation. However,
116 recent molecular studies showed that *T. grisea* can be found worldwide in the environmental, especially in water
117 supplies and humid conditions in northern Europe [6,14]. Thus, one could suggest that the foreign body which
118 was inoculated into the patient's left hand during the road accident, several years ago, likely represents the route
119 of infection. Thereafter, the immunosuppressive treatment became an adequate underlying condition to enhance
120 the development of the fungus, then subsequently generating local inflammation responsible for the macroscopic
121 lesion without developing grains.

122 In practice, curative therapy for superficial phaeohyphomycosis is closed to the management of fungal
123 mycetoma, based on oral antifungal drugs in first-line strategy, then on surgical excision (and, in some cases, on
124 cryotherapy). Guidelines from Chowdary *et al.* recommend oral antifungals, mainly azoles, as co-adjunctive
125 therapies particularly in immunocompromised patients and to prevent dissemination (recommendation BIII-

126 grade) [15]. In our case, an oral antifungal azole was not enough to allow complete or partial cure, so our
127 second-line strategy finally included extended-spectrum azole drugs added with terbinafine, because MICs of the
128 latter were demonstrated low for most dematiaceous fungi [12]. Terbinafine is actually a fungistatic agent that
129 inhibits the ergosterol synthesis of the plasma membrane of fungi. While its therapeutic role has been longtime
130 confined to treatment of dermatophyte infections, recent medical interest has been raised for subcutaneous or
131 refractory tropical fungal infection [16, 17]. A review of the literature [Table 1] showed 22 cases of
132 phaeohyphomycosis treated with terbinafine: 12 were successfully cured; in eight cases, terbinafine was
133 prescribed in first-line, including seven times in monotherapy (two patients underwent concomitant surgery).
134 Moreover, there were six cases of phaeohyphomycosis in solid organ recipients, including five who were cured
135 with terbinafine. Durations of treatment are poorly codified, but they often extend beyond several months or
136 even years [Table 1]. The main clinical results that one can expect consist in clearly delineating the lesion
137 through the prolonged antifungal therapy. This is supposed to make easier the surgical excision, and also to
138 reduce the subsequent risk of recurrence. A regular follow-up is encouraged throughout three years to ensure
139 complete clinical cure.

140

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143

144 **Disclosure**

145 All authors have seen and approved the manuscript. They all contributed significantly to the work. They have no
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266

267 **Figure legends**

268 **Figure 1** a) Aspect of the lesions on the dorsal side of the left hand, facing the third and fourth **Erreur ! Source**
269 **du renvoi introuvable.** extensor muscle's tendon; b) Aspect of the lesion after two months of treatment by
270 isavuconazole and terbinafine ointment on local apply; c) Aspect of the lesion after six month of treatment by
271 isavuconazole and terbinafine ointment on local apply, followed by six months of oral terbinafine.

272

273 **Figure 2** a) T1-weighted magnetic resonance imaging (MRI) of the left upper limb according to axial view
274 exhibited a cutaneous injury measuring approximately 32 x 11 mm with bone contact (shown by the yellow
275 arrow) but with neither bone edema nor osteitis; b) T1-weighted MRI of the left upper limb according to coronal
276 view showed a lesion facing the third and fourth **Erreur ! Source du renvoi introuvable.** extensor muscle's
277 tendon (shown by the yellow arrow)

278

279 **Figure 3** a) Histological observation according to HPS staining (Hematoxylin Phloxine Saffron) showed
280 inflammatory granulomatous giganto-epithelioid infiltrates, with polymorphonuclear cells and lymphocytes
281 developed near mycelial structures. No obvious criterion of malignancy was observed. b) Gomori-Grocott
282 methenamine silver staining, and c) PAS staining (Periodic Acid Schiff) preparations highlighted melanized
283 hyphae and beadlike swellings. No grains were seen, so the diagnosis of mycetoma was clearly rejected.

284

285 **Figure 4** Different colony morphologies (obverse and reverse) of *Trematosphaeria grisea* after ten days of *in*
286 *vitro* growth at 30°C. Colonies were velvety, a) light grey and radially folded on Sabouraud-dextrose agar; b)
287 light brown on oatmeal agar (OA); c) heaped with dark grey reverse on 2% malt extract agar (MEA) and d) light
288 tan on potato-dextrose agar (PDA).

289