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MAJOR ARTICLE

Ten-Year Experience of Cutaneous and/or Subcutaneous Infections Due to Coelomycetes in France

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Background. Coelomycetes are rarely but increasingly reported in association with human infections involving mostly skin and subcutaneous tissues, both in immunocompetent and immunocompromised patients. Coelomycetes constitute a heterogeneous group of filamentous fungi with distinct morphological characteristics in culture, namely an ability to produce asexual spores within fruit bodies.

Methods. We included all cases of proven primary cutaneous and/or subcutaneous infections due to coelomycetes received for identification at the French National Reference Center for Invasive Mycoses and Antifungals between 2005 and 2014. Eumycetoma, chromoblastomycosis, and disseminated infections were excluded.

Results. Eighteen cases were analyzed. The median age was 60.5 years. In all cases, patients originated from tropical or subtropical areas. An underlying immunodepression was present in 89% of cases. Cutaneous and/or subcutaneous lesions, mainly nodules, abscesses, or infiltrated plaques, were observed in distal body areas. Isolates of different genera of coelomycetes were identified: *Medicopsis* (6), *Paraconiothyrium* (3), *Gloniopsis* (3), *Diaporthe* (3), *Peyronellaea* (2), *Lasiodiplodia* (1). Lesion treatment consisted of complete (10) or partial (2) surgical excision and/or the use of systemic antifungal therapy, namely voriconazole (5) and posaconazole (4). Literature review yielded 48 additional cases of cutaneous and/or subcutaneous infections due to coelomycetes.

Conclusions. Infectious diseases physicians should suspect coelomycetes when observing cutaneous and/or subcutaneous infections in immunocompromised hosts from tropical areas; a sequence-based approach is crucial for strains identification but must be supported by consistent phenotypic features; surgical treatment should be favored for solitary, well limited lesions; new triazoles may be used in case of extensive lesions, especially in immunocompromised patients.

Keywords. coelomycetes; cutaneous phaeohyphomycosis; *Medicopsis romeroi*; *Paraconiothyrium* sp; subcutaneous abscess.

In the past 20 years, the incidence of community-acquired opportunistic infections has steadily risen, and invasive fungal diseases have become a growing source of morbidity and mortality. Rare and even new fungal species, among which melanized fungi and more specifically coelomycetes, are increasingly recognized as significant human pathogens [1].

Coelomycetes are a large and phylogenetically heterogeneous group of filamentous fungi that are grouped together on the basis of their asexual morphs in culture, ie, their ability to produce asexual spores known as conidia, within fruit bodies named conidiomata [2]. In both immunocompetent and immunocompromised patients, coelomycetes have been incriminated in various skin and soft tissue infections, namely cutaneous and subcutaneous phaeohyphomycosis, eumycotic black-grain mycetoma, and even 1 isolated case of chromoblastomycosis [3–6]. The term phaeohyphomycosis was initially coined in 1974 to describe various clinical manifestations caused by melanized fungi. It is defined by the presence of dematiaceous yeast-like cells, pseudo-hyphae-like elements, hyphae, or any combination of these in tissues [4].

In this study, we report 18 cases of cutaneous and/or subcutaneous infections due to coelomycetes that answer that description and can therefore be referred to as cutaneous and/or subcutaneous phaeohyphomycoses. Our aim was to (1) better characterize these rare fungal infections and their causative agents and (2) review treatment options.

MATERIAL AND METHODS

Inclusion and Exclusion Criteria

We performed a retrospective analysis of consecutive cases of cutaneous and/or subcutaneous infections due to coelomycetous

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fungi that were received for identification at the French National Reference Center for Invasive Mycoses and Antifungals (NRCMA) from 2005 to 2014. Cases were included if they fulfilled the following criteria: (1) proven infection according to the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) criteria with isolate recovery from abscess drainage, skin biopsy, or subcutaneous tissue samples; (2) absence of dissemination and microbiologically documented deep organ involvement (ie, primary cutaneous and/or subcutaneous infections). Cases of eumycetoma and chromoblastomycosis were excluded. A case of phaeohyphomycosis was defined by clinical findings consistent with that infection and either histopathological evidence of a melanized fungus or a culture positive for a melanized fungus and known agent of phaeohyphomycosis. Procedures were in accordance with the Helsinki Declaration.

Questionnaire and Pathological Analysis

A specific questionnaire was sent to collect epidemiological, clinical, mycological, and therapeutic data as well as follow-up information. Missing information and ambiguous answers were checked by phone with the physician and microbiologist. Tissue biopsies and histological sections (hematoxylin-eosin [HE], Gomori methenamine silver, and periodic acid-Schiff [PAS] stainings) were obtained from pathology laboratories and reanalyzed by a dermatopathologist. When necessary, Fontana-Masson staining was performed to visualize hyphae pigmentation.

Mycological Identification

According to standard practice at the NRCMA, species identification was performed by a polyphasic approach. The purity of all isolates was checked by obtaining single isolated colonies on Sabouraud chloramphenicol agar medium. Colonies were subcultured onto 2% malt agar, potato carrot agar (PC), oatmeal agar (OA) tubes, or autoclaved straw pieces on 2% water agar plates and incubated at 30°C under near-ultraviolet light or at 25°C to promote sporulation. Microscopic preparations were mounted in cotton blue from cultures sporulating on the different media. Molecular identification was performed by sequencing the ITS1-5.8S-ITS2 (ITS) region of the ribosomal deoxyribonucleic acid (rDNA), the D1-D2 domain of the large subunit rDNA (28S), and a small region of the elongation factor (EF)-1α and of the β-tubulin (TUB) genes (described in Supplementary Data).

Antifungal Susceptibility Determination

In vitro susceptibility testing was performed according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) procedure [7] with some modifications [8]. Seven antifungal agents were included: amphotericin B, triazoles (itraconazole, voriconazole, posaconazole), echinocandins (caspofungin, micafungin), and terbinafine. All strains were subcultured on PC or OA for 7 to 30 days at 25°C and 30°C. Conidia were then collected in water, and the suspension was adjusted to $2–5 \times 10^5$ colony-forming units/mL.

Review of Reported Cases

We reviewed all cases of cutaneous and/or subcutaneous infections due to coelomycetes published in the literature from 1970 to 2015, excluding eumycetoma and chromoblastomycosis. The keywords used for this search were as follows: phaeohyphomycosis, and cutaneous, subcutaneous, abscess, cyst, skin, coelomycetes, *Phoma*, *Pleurophoma*, *Rhytidhysteron rufulum*, *Medicopsis romeroi*, *Pyrenochaeta*, *Paraconiothyrium*, *Phomopsis*, *Pleurophomopsis*, *Lasiodiplodia*, *Colletotrichum*, *Coniothyrium*, *Microsphaeropsis*, *Nattrassia mangiferae*, *Gloniopsis*, and *Diaporthe*.

RESULTS

Epidemiological Characteristics of the Patients

Among a total of 31 fungal infections due to coelomycetes and received for identification at the NRCMA, 18 cases of proven cutaneous and/or subcutaneous infections were analyzed (Table 1). Patients' median age was 60.5 years (47–78 years). The sex ratio was 3.5:1 (14 of 18, ie, 78% of patients were male).

Geographical Distribution

Patients all originated from tropical and subtropical regions, and most had traveled there in the past 18 months: Africa (10 cases), Asia (3 cases), West Indies (5 cases). Five patients (28%) were from rural areas, engaged in farming or with a history of soil or plant trauma 1 to 3 months before lesion appearance. However, 3 immunocompromised patients without trauma history had not left France for 5 to 10 years before lesion appearance.

Underlying Diseases and Risk Factors

Underlying diseases were reported in 16 cases (89%). Nine patients (50%) received solid organ transplants (SOT) (8 kidneys, 1 liver); 6 patients suffered from diabetes mellitus, and 2 patients suffered from hematological malignancies. Topical/oral steroids and immunosuppressive agents (mycophenolate mofetil, tacrolimus, cyclosporine) were used in 11 and 9 cases, respectively. Two patients (11%) had no apparent underlying disease.

Clinical Signs and Symptoms

Fourteen patients (patients 1 to 14) displayed subcutaneous lesions, usually 1 solitary nodule (Figure 1), sometimes associated with local inflammation and mimicking an abscess (8 cases). One patient had multiple cutaneous and subcutaneous lesions on the knee (patient 13; Figure 2), and 1 patient had an aponeurotic cyst (patient 14). Three patients (patients 15 to 17) presented with a cutaneous form of the disease, exhibiting infiltrated, pigmented, budding, or necrotic plaques, scaly and wart-like when localized on the foot sole. Solitary lesions were the most frequent (12 patients, 67% of cases). Two patients displayed concomitant cutaneous/subcutaneous infections

Table 1. Clinical and Epidemiological Characteristics of 18 Human Cutaneous and/or Subcutaneous Infections Due to Coelomycetes Seen Between 2005 and 2014 in France

Patient	Sex, Age (Years)	Injury History	Geographical Area	Underlying Risk Factors	Lesion Type	Body Site (Lesion Characteristics)	Histology	Direct Microscopic Examination	Culture	Treatment		Outcome	Follow-Up
										Agent (Dosage, mg/day, Duration)	Surgery		
1	F, 59		Sri Lanka/ France	Diabetes mellitus/ Polymyalgia rheumatica Prednisone	Subcutaneous	Foot (1 nodule)	Pigmented hyphae, gran inf	Hyphae	*Medicopsis romeroi*	None	Total excision	Cured	8 y
2	F, 73		India/France	Giant cell arteritis Prednisone	Subcutaneous	Foot (1 abscess), leg (2 cystic nodules)	Pigmented hyphae, gran inf	Negative	*M romeroi*	VCZ (400, 3 wk)	Total excision	Cured	7 y
3	M, 65		West Africa /France	Renal graft IS therapy: Tac, MMF, prednisone	Subcutaneous	Knee (1 abscess)	Aspecific chronic inf	Negative	*M romeroi*	POSA (800, 1 mo)	None	Cured	6 y
4	F, 47		West Africa /France	Diabetes mellitus	Subcutaneous	Foot (1 abscess)	Pigmented hyphae, gran inf	Not done	*M romeroi*	None	Total excision	Cured	1 y
5	M, 53		Pakistan /France	Liver graft IS therapy: Tac, MMF, prednisone	Subcutaneous	Foot (1 abscess)	Not done	Hyphae	*M romeroi*	POSA (800, 2 wk) followed by LAMB (3 mg/ kg, 2 mo)	2 abscess drainages	Relapse under POSA. Cured by LAMB + total excision	10 mo
6	M, 54	Farmer / injury	West Indies/ France	Chronic hepatitis C	Subcutaneous	Forearm (1 abscess)	Pigmented hyphae, gran inf	Hyphae	*Gloniopsis* sp	None	Total excision	Cured	8 y
7	M, 63		West Africa /France	Renal graft IS therapy: cyclosporine	Subcutaneous	Hand (1 abscess)	Not done	Hyphae	*Gloniopsis* sp	POSA (800, 2 mo)	Relapse treated by total excision	Relapse 19 mo after POSA. Cured by excision	5 y
8	M, 53	Sheperd /injury	West Africa /France	Acute B-cell leukemia, neutropenia	Subcutaneous	Finger (1 infiltrated plaque), foot (2 abscesses)	Not done	Hyphae	*Peyronellaea gardenia*	LAMB (3 mg/kg, 6 wk) followed by VCZ (400, 6 wk)	None	Cured	6 y
9	M, 58	Farmer	West Africa /France	Renal graft IS therapy: Tac, MMF, prednisone Diabetes mellitus	Subcutaneous	Foot (1 abscess)	Pigmented hyphae, gran inf	Hyphae	*P gardeniae*	VCZ (400, 13 mo)	Total excision	Cured	5 y
10 [9]	M, 71	Gardener	West Indies (Guadeloupe) /France	Renal graft IS therapy: Tac, MMF, prednisone	Subcutaneous	Elbow (1 nodule)	Not done	Hyphae	*Paraconiothyrium cyclothyrioides*	LAMB (3 mg/kg, 4 wk) and VCZ (400, 7 wk)	None	Died of underlying condition	2 mo
11	M, 78		West Indies (Guadeloupe)	Diabetes mellitus	Subcutaneous	Foot (1 nodule)	Not done	Hyphae	*Diaporthe* sp	ITRA (200, 18 mo)	None	Relapse 6 mo after ITRA	2 y
12	M, 51	Foot trauma	West Africa /France	Renal graft IS therapy: Tac, MMF, prednisone Diabetes mellitus	Subcutaneous	Finger (1 nodule), foot (2 nodules)	Pigmented hyphae, gran inf	Hyphae	*Diaporthe raonikayaporum*	None	Total excision	Cured	2 y

Table 1 continued.

Patient	Sex, Age (Years)	Injury History	Geographical Area	Underlying Risk Factors	Lesion Type	Body Site (Lesion Characteristics)	Histology	Direct Microscopic Examination	Culture	Treatment: Agent (Dosage, mg/day, Duration)	Treatment: Surgery	Outcome	Follow-Up
13	M, 62		West Africa /France	Renal graft IS therapy: Tac, prednisone	Subcutaneous	Knee (multiple nodules with diffuse skin infiltration)	Pigmented hyphae, gran inf	Hyphae	*Ascomycete order Pleosporales*	POSA (800, 4 y)	3 rounds of partial excision	2 early relapses in the first 6 mo	4 y
14	M, 70		West Africa /France	None	Subcutaneous	Elbow (1 aponeurotic cyst)	Pigmented hyphae, gran inf	Not done	*Gloniopsis* sp	None	Total excision	Cured	3 mo
15	M, 55		La Réunion/ France	Renal graft IS therapy: Tac, MMF, prednisone Diabetes mellitus Chronic hepatitis B and C/cirrhosis	Cutaneous	Foot sole (1 pigmented budding infiltrated plaque with central nodule)	Pigmented hyphae, gran inf	Hyphae	*P cyclothyrioides*	LAMB (3 mg/kg, 4 wk) and Caspofungin (50, 1 wk)	None	Died of underlying condition	1 mo
16 [10]	M, 68		West Indies (Martinique)	B cell lymphoma, chemotherapy, methylprednisolone, neutropenia	Cutaneous	Foot sole (1 pigmented infiltrated plaque)	Not done	Hyphae	*P cyclothyrioides*	VCZ (200, 10 wk) and corticosteroids discontinuation	None	Lesion regression. Died of underlying condition	3 mo
					Cutaneous	Heel (1 pigmented infiltrated plaque)	Not done	Hyphae	*Diaporthe sojae*				
17 [11]	M, 66		Central Africa /France	Renal graft IS therapy: Tac, MMF, prednisolone	Cutaneous	Foot sole (1 plantar wart)	Pigmented hyphae, gran inf	Hyphae	*M romeroi*	Reduction of IS therapy	total excision	Cured	4 y
18	F, 47		West Indies (Martinique)	2nd/3rd degree burn lesions over 60% of total BSA	Cutaneous	Forearm (3d degree necrotic burn lesion)	Not done	Negative	*Lasiodiplodia theobromae* species complex	None	Excision of necrotic tissues	Died of underlying condition	2 wk

Abbreviations: BSA, body surface area; gran, granulomatous; inf, inflammation; IS, immunosuppressive; ITRA, itraconazole; LAMB, liposomal amphotericin B; MMF, mycophenolate mofetil; POSA, posaconazole; Tac, tacrolimus; VCZ, voriconazole.

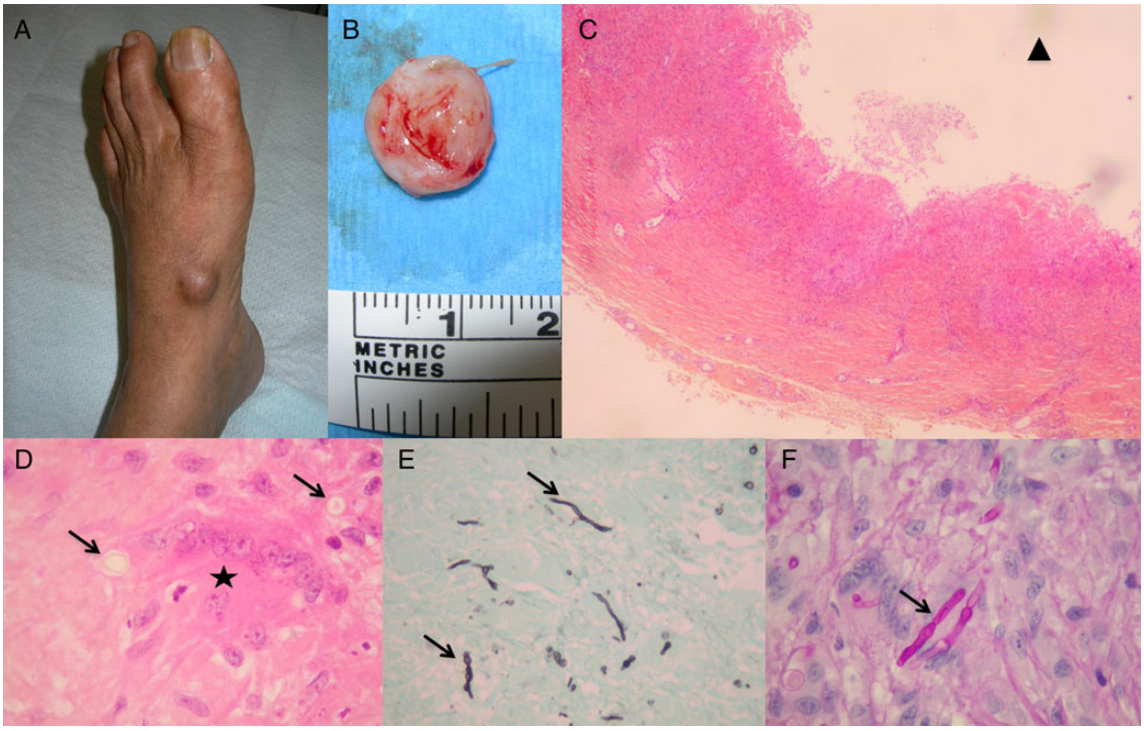

Figure 1. Patient 1. (A and B) Painless subcutaneous cyst of the left foot containing a puriform liquid in a 59-year-old woman with polymyalgia rheumatica treated by corticosteroid therapy. (C) Hematoxylin-eosin staining showed a deep dermal abscess mixed with granulomatous inflammation (×40). The black triangle labels the cyst lumen. (D) Hematoxylin-eosin staining (×1000) with high magnification of a multinucleated cell (black star) and pigmented fungal hyphae (black arrows) (×1000). (E) Gomori methenamine silver stain and (F) periodic acid-Schiff staining ([E], ×400; [F], ×1000) revealed globose or elongated septate hyphal elements (black arrows).

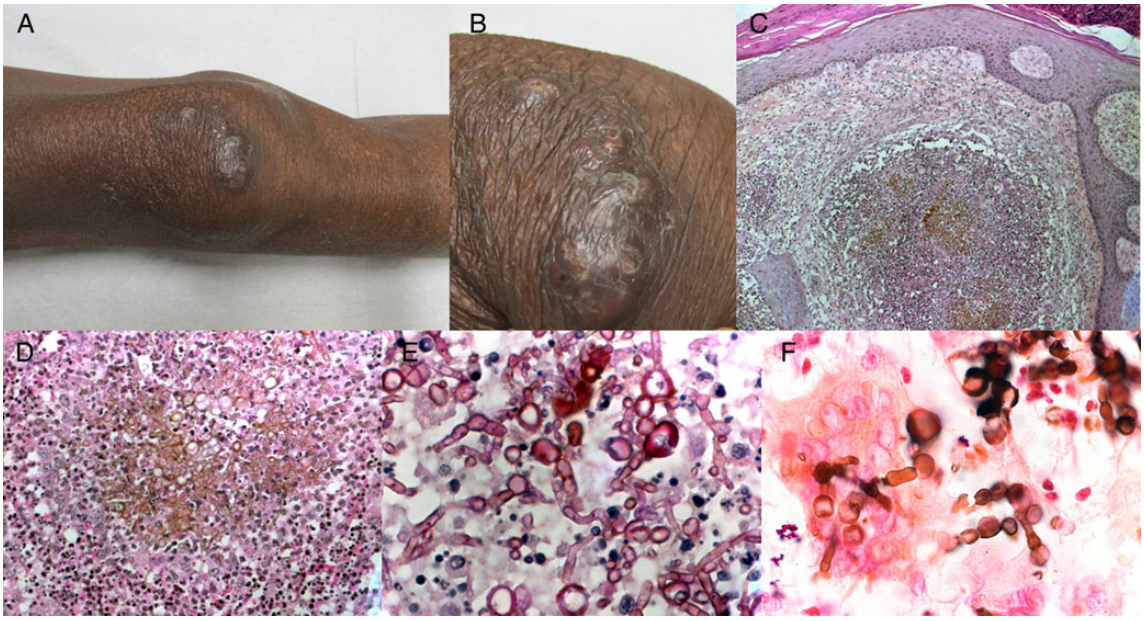

Figure 2. Patient 13. Pigmented infiltrated plaque of the right knee associated with diffuse subcutaneous infiltration in a 62-year-old kidney transplant recipient. (A) Full and (B) close-up views (courtesy of Camille Frances). (C and D) Hematoxylin-eosin staining revealed a dense dermal infiltrate with granulomatous inflammation, associating neutrophils, lymphocytes, epithelioid, and multinucleated cells, as well as pigmented fungal hyphae ([C], ×100; [D], ×400). (E) Periodic acid-Schiff staining showed septate fungal hyphae (×1000). (F) Fontana-Masson staining confirmed the pigmented character of fungal structures (×1000).

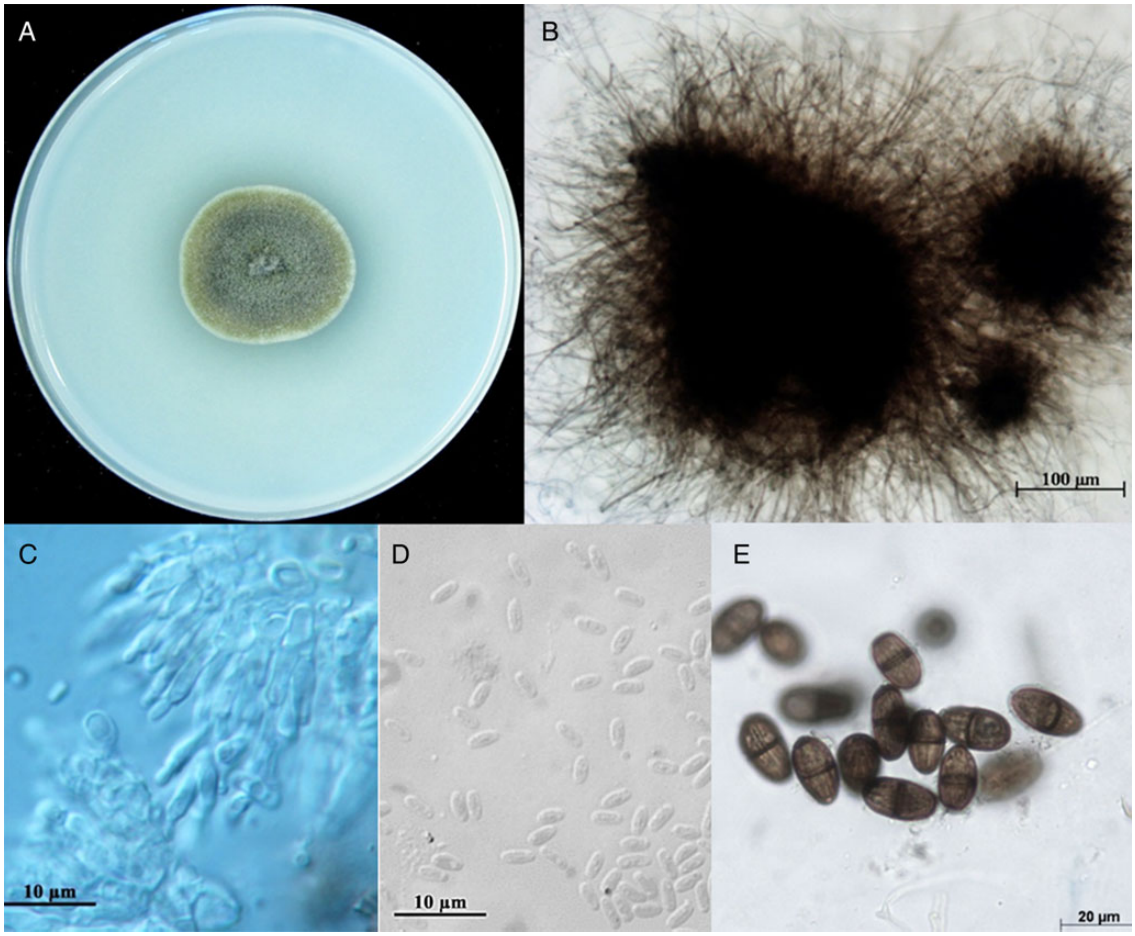

Figure 3. Macroscopic aspect of *Medicopsis romeroi* on oatmeal agar (OA), 28°C, 14 days (A); immersed pycnidium of strain CNRMA11.1115 on OA medium (B); conidiophores and conidiogenous cells from a pycnidium of *M romeroi* (C) small, hyaline conidia of *Gloniopsis* sp strain (D); mature, septate, striated conidia of *Lasiodiplodia theobromae* species.

involving 2 (*Paraconiothyrium cyclothyrioides* and *Phaeoacremonium parasiticum* [9], patient 10) or 3 fungi (*Phomopsis longicolla* reidentified as *Diaporthe sojae*, *P cyclothyrioides* and *Cunninghamella bertholletiae* [10], patient 16). Lesions involved exclusively distal areas of the upper limbs in 7 cases (39%) and the lower limbs in 13 cases (72%). The foot was the site most frequently involved (14 lesions).

In all 11 cases in which a pathological examination of skin tissue was performed, an aspect highly suggestive of infection was observed with a granulomatous dermal infiltrate containing epithelioid and multinucleated giant cells. In 10 of 11 cases, stainings revealed elongated septate and branched hyphae or globose fungal structures (HE, PAS, and Gomori methenamine silver stainings; Figures 1 and 2). Pigmentation of the fungal structures was confirmed using HE and Fontana-Masson stainings.

Mycological Identification

Twenty-two isolates were available for the 18 patients, but the same fungus was identified in the 4 cases in which we had 2 isolates. Microscopy of the initial cultures revealed septate-melanized hyphae in the majority of isolates (Figure 3). Pycnidial conidiomata were seen for 13 of 22 isolates after at least 3 weeks of subculture on special media (Supplementary Table S1). In parallel, a multilocus sequence-based analysis was performed for all clinical isolates, resulting in the identification of 11 isolates to the species level: *M romeroi* (6 cases), *P cyclothyrioides* (3 cases), *Diaporthe raonikayaporum* (1 case), and *D sojae* (1 case). Identification to the genus level was achieved for 4 isolates: *Diaporthe* sp (1 case) and *Gloniopsis* sp (3 cases). One isolate belonged to the *Lasiodiplodia theobromae* species complex, and a possible identity of *Peyronellaea gardeniae* was found for 2 isolates. Finally, the identity of isolate CNRMA11.1115 remained uncertain due to the absence of sequence entries on the curated databases for known taxa (Supplementary Table S1).

In Vitro Antifungal Susceptibility Testing

Minimum inhibitory concentrations (MICs) were determined for the 11 strains that produced enough conidia (Supplementary Table S2). Low MICs of amphotericin B (0.06 to 1 µg/mL),

Table 2. Clinical and Epidemiological Characteristics of Reported Human Cutaneous and/or Subcutaneous Infections Due to Coelomycetes

Author (and Reference)	Year of Report	Sex, Age in Years	Injury History	Geographical Area	Underlying Risk Factor	Type of Lesion (SC or C)	Body Site	Culture	Treatment	Outcome	Follow-Up[a]
Bakerspigel [S2]	1970	F, 22	Farmer	Ontario, Canada	Topical steroids	C: Erythematous nodule with pustular lesions	Leg	*Phoma hibernica*	Oral griseofulvin	Regression	5 y
Young [S3]	1973	F, 42		Jamaica/ United States	Renal transplant	SC: Subcutaneous cystic lesion	Heel	*Phoma* sp	Excision	Cured	6 mo
Gordon [S4]	1975	M, 4			None	C: Superficial crusted lesion	Ear	*Phoma* sp	Oral griseofulvin	Cured	ND
Bakerspigel [S5]	1981	M, 1.5		Ontario, Canada	None	C: Perioral crusted lesion	Face	*Phoma eupyrena*	Topical clotrimazole	Cured	2 y
Shukla [S6]	1984	F, 18		India	Typhoid fever	C: Superficial papulovesicular lesions	Face	*Phoma minutispora*	Topical clotrimazole	Cured	1 mo
Shukla [S6]	1984	M, 20	Farmer	India	Corticosteroids (chronic sinusitis)	C: Superficial maculopapules	Neck	*P minutispora*	Topical clotrimazole	Cured	20 d
Baker [S7]	1987	M, 75	Farmer	Dominican Republic	Diabetes mellitus/ Corticosteroids (myasthenia gravis)	SC: Subcutaneous lesion	Foot	*Phoma minutella*	Amputation	Cured	1 y
Stone [S8]	1988	M, 25		Texas	None	SC: Subcutaneous cystic lesion	Forearm	*Phoma* sp	Excision/Oral ketoconazole	Cured	15 mo
Dooley [17, 18]	1989	F, 56	Gardener	Texas	Diabetes mellitus/ Cardiac transplant	SC: Subcutaneous nodules	Thigh, knee, wrist	*Pleurophoma pleurospora* Reclassified as *Paraconiothyrium maculicutis*	Excision/ Topical miconazole	Cured	ND
Rai [S9]	1989	M, 24		India	None	C: Superficial papulovesicular lesions	Face, neck, hands	*Phoma sorghina*	Topical miconazole	Cured	1 mo
Rai [S9]	1989	M, 19		India	None	C: Superficial macular lesions	Face	*P sorghina*	Topical miconazole	Cured	1 mo
Chabasse [S10]	1995	M, 74	Farmer	France	Corticosteroids (asthma)	SC: Subcutaneous abscess	Leg	*Pleurophomopsis lignicolla* Petr	Excision. Relapse treated by a second excision.	Relapse after 12 mo.	12 mon
Rosen [S11]	1996	F, 24	Vacations on a farm	Texas	Topical steroids	C: Infiltrated plaque	Face	*Phoma* sp	Oral ketoconazole	Cured	2 y
Hirsh [S12]	1996	M, 45	Farmer	Hawaii	None	C: Infiltrated plaque, nodules	Hand	*Phoma* sp	Oral itraconazole	Regression	ND
Maslen [S13]	1996	F, 40	Intramuscular injections in buttock	Cambodia/ Australia	None	SC: Indurated plaque with central subcutaneous abscess	Buttock	*Lasiodiplodia theobromae*	Debridement	Cured	5 mo
Zaitz [S14]	1997	M, 63		Brazil	Corticosteroids (sarcoidosis)	C: Infiltrated plaque, nodules	Sternal region, hand	*Pleurophoma cava*	Amphotericin B/Oral itraconazole	Cured	ND
Arrese [S15]	1997	M, 53	Owner of a bakery	Morocco/ Belgium	Topical steroids/Short corticosteroid therapies (urticaria, hay fever)	C: Scaly plantar lesion	Foot	*Phoma* sp	Topical bifonazole/ topical ketoconazole	Persistence	Lost to follow-up

Table 2 continued.

Author (and Reference)	Year of Report	Sex, Age in Years	Injury History	Geographical Area	Underlying Risk Factor	Type of Lesion (SC or C)	Body Site	Culture	Treatment	Outcome	Follow-Up[a]
Sigler [19]	1997	M, 73		Arizona	Diabetes mellitus/ Corticosteroids therapy	SC: Subcutaneous abscesses and infiltrated plaques	Arm, forearm	*Nattrassia mangiferae*	Topical miconazole/ Amphotericin B	Relapse	ND
Guarro [S16]	1998	M, 56	Farmer, traumatic injury	Brazil	Diabetes mellitus/ corticosteroids	SC: Several nodular solitary or confluent lesions, macular lesions	Forearm, elbow	*Colletotrichum gloeosporioides*	None	Persistence	Died of other cause
Oh [S17]	1999	M, 77	Farmer	Korea	Topical steroids	C: Indurated plaque	Forearm	*Phoma* sp	Oral itraconazole	Regression	ND
Guarro [S18]	1999	F, 59		Spain	None	C: Scaly, infiltrated plaque with inflammatory border	Shoulder	*Microsphaeropsis olivacea*	Topical clotrimazole/ oral terbinafine	Cured	7 mo
O'Quinn [20]	2001	M, 34	Cactus inoculation	Tennessee	Acute lymphocytic leukemia/ Chemotherapy	SC: Subcutaneous tender nodule	Forearm	*C gloeosporioides*	Amphotericin B followed by oral itraconazole	Cured	ND
O'Quinn [20]	2001	M, 47		Mississippi	Non-Hodgkin lymphoma/ Chemotherapy/ autologous stem cell transplantation	SC: Subcutaneous tender nodule with central pustule	Arm	*Colletotrichum coccodes*	Amphotericin B followed by oral itraconazole	Cured	ND
Castro [S19]	2001	M, 34	Gardener	Brazil	Renal transplant	SC: Subcutaneous nodule	Leg	*Colletotrichum crassipes*	Total excision	Cured	ND
Miele [S20]	2002	M, 60	Gardener	Washington DC	Diabetes mellitus/Renal transplant	SC: Subcutaneous abscess	Knee	*Coniothyrium-Microsphaeropsis complex*	Broad debridement/ Oral itraconazole	Cured	ND
Girard [S21]	2004	M, 45		West Africa/ France	Leprosy	SC: Multiple painful non-inflammatory subcutaneous nodules	Legs (2), foot (2)	*Pyrenochaeta romeroi*	Surgical excision/ Abscess drainage/ oral itraconazole	Cured	1 y
Summerbell [S22]	2004	F, 50	Outdoor injury	Jamaica	None	SC: Ulcer	Leg	*Lasiodiplodia theobromae*	Broad debridement	Cured	6 mo
Siu [S23]	2004	M, 49	Traumatic abrasion	Hawaii	Diabetes mellitus/Heart transplant	SC: Annular and nodular plaques	Legs, Knees	*Coniothyrium-Microsphaeropsis* complex	Several relapses following excision and oral treatment (fluconazole, itraconazole). Treated by excision and Amphotericine B	Cured	4 mo
Godoy [S24]	2004	M, 65	Lived in rural area	Brazil	None	C: Desquamative interdigital lesions	Feet	*N mangiferae*	ND	ND	ND
Padhye [S25]	2004	M, 41		West Africa	Diabetes mellitus/AIDS/ chronic hepatitis/active tuberculosis	SC: Tender, mobile, subcutaneous abcess	Arm	*Pleurophomopsis lignicolla*	Abscess drainage	Healed	ND

Table 2 continued.

Author (and Reference)	Year of Report	Sex, Age in Years	Injury History	Geographical Area	Underlying Risk Factor	Type of Lesion (SC or C)	Body Site	Culture	Treatment	Outcome	Follow-Up[a]
Pendle [S26]	2004	M, 80		Australia	Diabetes mellitus/ Inflammatory demyelinating polyneuropathy/ Immunosuppressive therapy	C: Painless granulomatous plaque	Hand	*Microsphaeropsis arundinis*	Terbinafine	Cured	2.5 y
Pendle [S26]	2004	M, 56		Australia	Diabetes mellitus/ Ankylosing spondylarthropathy/ Immunosuppressive therapy	SC: Necrotic ulcers	Feet	*M arundinis*	Amputation and itraconazole	Cured	10 mo
Suh [S27]	2005	M, 19		Korea	Unknown status	C: Verrucous plaque	Face	*Phoma* sp	AmB	Regression	ND
Balajee [21]	2007	M, 3		ND	Liver transplant	C: Crusted nodules	Leg	*Paraconiothyrium cyclothyrioides*	ND	ND	ND
Badali [22]	2010	F, 45		India	None	SC: Verrucous plaque, subcutaneous cyst	Forearm	*Pyrenochaeta romeroi*	Excision	Cured	1 y
Khan [S28]	2011	F, 47		India/ Kuwait	Acute lymphoblastic leukemia/Chemotherapy	SC: Subcutaneous nodule with central necrosis	Finger	*P romeroi*	Cyst drainage	Partial regression	ND
Gordon [23]	2012	M, 49		Texas	Renal transplant/ Diabetes mellitus	C: Crusted ulcerated plaques	Legs	*P cyclothyrioides*	No response to Voriconazole. Posaconazole	Cured	ND
Severo [S29]	2012	M, 53		Brazil	Lung transplant	SC: Necrotic ulcerated subcutaneous cyst	Knee	*C gloeosporioides*	Total excision	Cured	Died
Mattei [24]	2013	M, 43	Farmer	Brazil	Renal transplant/ Diabetes mellitus	C: Indurated plaques	Arm, leg	*Diaporthe phaseolorum*	Oral itraconazole and surgical excision	Cured	5 mo
Hsiao [25]	2013	M, 78	Farmer	Taiwan	None	C: Verrucous plaque	Forearm, dorsal hand	*P romeroi*	No response to oral itraconazole and surgical excision. Amphotericin B	Cured	6 mo
Hall [S30]	2013	M, 70		Florida	Renal transplant	C: Crusted, ulcerated plaque and papules	Finger, forearm	*M arundinis*	Posaconazole	Cured	6 mo
Mahajan [26]	2014	M, 72		India	Diabetes mellitus	SC: Subcutaneous swelling	Foot	*Rhytidhysteron rufulum*	No response to a combination of surgical excision, itraconazole and terbinafine. Intralesional liposomal amphotericin B	Cured	1 y

Table 2 continued.

Author (and Reference)	Year of Report	Sex, Age in Years	Injury History	Geographical Area	Underlying Risk Factor	Type of Lesion (SC or C)	Body Site	Culture	Treatment	Outcome	Follow-Up[a]
Chan [S31]	2014	M, 55		China	Renal transplant	SC: Painless nodular subcutaneous cyst	Thigh	*P romeroi*	Several relapses after repeated attempts at total excision. Oral Itraconazole continued until death.	Relapse after tapering of itraconazole. Remission on resuming full dose.	5 y
Ogawa [S32]	2014	M, 68		Brazil	Renal transplant	SC: Papulo-nodular lesion	Finger	*C gloeosporioides*	Total excision	Cured	1 y
Asahina [27]	2015	F, 57		Japan	Systemic lupus erythematosus Autoimmune hepatitis Immunosuppressive therapy	C: Erythematous scaling plaques and nodules	Finger, forearm, knee, leg, abdomen	*M arundinis*	Itraconazole, fluconazole, liposomal amphotericin B ineffective. Local thermotherapy.	Resolution after local therapy	ND
Asahina [27]	2015	F, 74		Japan	Temporal arteritis Hypogammaglobulinemia Immunosuppressive therapy Diabetes mellitus	C: Erythematous indurated plaques and papules	Hand	*M arundinis*	Itraconazole and local thermotherapy.	Regression	ND
Papacostas [S33]	2015	M, 59	Inoculation	Kenya/ Australia	None	SC: Subcutaneous swelling	Foot	*Lasiodiplodia theobromae*	Excision and Voriconazole.	Cured	3 mo
Yadav [S34]	2015	F, 50		India	Diabetes mellitus	SC: Painless subcutaneous cyst	Foot	*P romeroi*	Drainage and Itraconazole	Cured	3 mo

Abbreviations: AIDS, acquired immune deficiency syndrome; AmB, amphotericin B; C, cutaneous; ND, not described; SC, subcutaneous.

voriconazole (0.03 to 0.5 μg/mL), and terbinafine (0.06 to 1 μg/mL) were observed for all the strains tested with the exception of species CNRMA13.515, which exhibited a terbinafine MIC of 4 μg/mL. The *P cyclothyrioides* and the 2 *P gardeniae* isolates exhibited low MICs of all antifungals tested except for echinocandins and posaconazole, respectively. The 3 *M romeroi* strains and the 1 belonging to the *L theobromae* species complex had high itraconazole MICs (4 to ≥8 μg/mL). The lowest triazole and echinocandin MICs were observed for *P cyclothyrioides* and *D sojae*, respectively.

Treatment and Follow-Up

Systemic antifungals were prescribed in 11 of the 18 cases (61%) for a median duration of 2.5 months: voriconazole (5 cases), posaconazole or liposomal amphotericin B (4 cases each), and itraconazole (1 case). In 1 patient, liposomal amphotericin B therapy was followed by voriconazole administration. Another patient was switched to liposomal amphotericin B after 2 weeks of inefficient posaconazole treatment. Liposomal amphotericin B was combined with caspofungin or voriconazole (1 case each). Six patients were treated by antifungals alone. Surgery was performed in 12 patients: total excision (10 cases) or partial excision (2 cases). It was the sole treatment in 7 cases (39%).

The mean follow-up was 36 months (2 weeks–96 months). Four patients (22%) died of the underlying disease during the first 3 months. Regression or complete cure was obtained in 13 of the remaining 14 cases where follow-up was available. Seven patients were cured by excision alone, which was the first-line treatment in 6 cases. Of the 6 patients treated by antifungal drugs only, 2 relapsed. Of note, patient 7 relapsed 19 months after a 2-month treatment with posaconazole and was cured by total excision of the relapsing solitary lesion. Of the 4 patients treated by combined surgery and antifungals, 2 patients relapsed but were eventually cured by a second or third line of combined treatment. The diffuse subcutaneous infiltration of the lower limb of patient 13 was controlled by the combination of 3 partial surgical procedures and a prolonged high-dose regimen of posaconazole.

DISCUSSION

Coelomycetes correspond to an artificial group of ascomycete and few basidiomycete fungi able to produce spores (conidia) within fruit bodies (conidiomata) [6, 12]. To date, approximately 1000 genera and 7000 species are included in this group [13]. These fungi have been reported as plant pathogens [14] and implicated in animal and human infections [6, 15]. However, in the past, reports have been limited by the lack of correct identification of these pathogens [1]. The ongoing taxonomical reorganization of some groups of coelomycetes is an additional issue.

Melanized fungi are involved in proven infections in both immunocompromised and immunocompetent individuals. In a review of 72 disseminated phaeohyphomycoses, infection was associated with some degree of immune dysfunction in 76% of patients [16]. Similarly, 89% of our 18 patients were immunocompromised, with 50% of SOT recipients. Our literature search yielded 48 published cases of cutaneous and/or subcutaneous infections (excluding eumycetoma and chromoblastomycosis) attributed to coelomycetes, among which 29 (60%) occurred in immunocompromised patients, including 12 (25%) organ transplant recipients (Table 2). It is interesting to note that 2 patients (patients 10 and 16) in our series displayed multiple concomitant fungal infections, a finding that underlines the favoring role of immune suppression in the emergence of these mycoses.

All 18 of our cases occurred in patients originating from tropical and subtropical areas, conversely to literature review with only 29 of 48 (60%) patients living in tropical and subtropical regions (Table 2). Indeed, 14 (29%) cases were described in North American countries, United States (mostly southern states), Canada, or European countries (Italy, Spain, France). Four (8%) cases were reported in Northern Asia (Korea, Japan).

Coelomycete infections are frequently reported after inoculation or in patients from rural areas engaged in farming (28% of our patients; 39.5% [19 of 48] of literature cases). In our series, lesions involved mostly distal parts of the limbs, with foot involvement in 11 (61%) patients. Likewise, most of the 48 published cases occurred on exposed areas (face, neck, legs, and arms). These findings are suggestive of the role of minor trauma and inoculation, which is compatible with an environmental source of these fungi. Delay between inoculation and disease may depend on the inoculum size, the extent of the injury sustained, and the underlying disease. Coelomycetes are incriminated as well in keratitis, with case reports suggesting the role of corneal trauma [28]. Rare synovium or lung infections have also been reported [29, 30].

Until recently, the study of coelomycetes phylogeny was based on classic taxonomy that relied on morphology. However, some important distinctive morphological characteristics (conidiation or pigmentation) are inconstant when fungi are cultured on artificial media, rendering phenotypical identification of genera and species difficult. The introduction of molecular techniques such as the sequencing and analysis of fungal ribosomal operons (ITS, 28S) and several protein-coding genes (actin, TUB, EF-1, calmodulin, etc) has considerably helped in resolving species complexes and generic boundaries of some coelomycetes [31–37], resulting in a complete taxonomical reorganization. Many genera still have to be analyzed using only molecular techniques [12]. By now, the mycological community should be aware that important nomenclatural changes are taking place since the publication of the "Amsterdam Declaration of Fungal Nomenclature" [38], which in part abolished the separate naming of anamorphs and teleomorphs of the same fungus. The following online databases may be helpful for clarification of the

presently accepted names of fungal species (http://www.mycobank.org/ http://www.indexfungorum.org).

In this study, we performed a polyphasic approach that takes into account morphological features, cultural characteristics, and several molecular targets. However, 7 of the strains could not be identified to the species level due to lack of sporulation, despite the test of varied culture conditions and lack of sequence homology in the public databases. These strains are now included in an ongoing taxonomical study describing novel taxa in coelomycetes.

Nevertheless, in this study, we report new emerging pathogens. *Gloniopsis* sp was isolated in 3 patients and to date had never been reported as agent of cutaneous or subcutaneous infections. *Paraconiothyrium cyclothyrioides*, here incriminated in 3 cases of cutaneous plaques or abscesses, was previously described in only 2 cases of skin lesions [21, 23]. Of note, a reported case involving *Paraconiothyrium maculicutis* had initially been identified as *Pleurophoma pleurospora* [17, 18]. The most frequently isolated coelomycete in our series (6 cases) was *M romeroi*, previously named *Pyrenochaeta romeroi*. This fungus is usually associated with eumycetomas [6]. Only 6 additional cases of phaeohyphomycoses have been attributed to this fungus (Table 2).

Limited data on the in vitro antifungal susceptibilities of coelomycetes are available in the literature, mainly inferred from clinical cases, with potential variations due to the use of different methodologies [2, 3, 22]. Here all strains were tested using a microdilution method slightly adapted from EUCAST [7, 8]. Knowing the extreme phylogenetic diversity of these fungi, we were not surprised to see marked differences in the in vitro susceptibility results according to genus and species, keeping in mind that there are no defined EUCAST breakpoints for coelomycetes and no established correlation between MIC and clinical outcome. Nevertheless, low MIC values were uniformly obtained for voriconazole. These results are in line with Ahmed et al [39] study.

Treatment of coelomycete infections is obviously not standardized. In the literature, therapeutic management varies according to clinical presentation (subcutaneous vs cutaneous). The vast majority (20 of 25) of subcutaneous forms (described as abscesses, cystic lesions or ulcers) were treated by excision or drainage (Table 2). Surgery was the only treatment in 11 of the 20 cases, whereas it was combined with antifungal therapy in 9 cases (itraconazole [7 cases], amphotericin B [2 cases], or ketoconazole, terbinafine, fluconazole, voriconazole [1 case each]). Excision combined with itraconazole followed by terbinafine failed for 1 infection due to *R rufulum*, which was eventually cured by intralesional amphotericin B injections [26]. The remaining subcutaneous cases were successfully treated by antifungal therapy alone: systemic amphotericin B therapy (3 cases) followed or not by itraconazole [19, 20]. In our series, surgery was performed in 10 of 14 (71%) cases, either alone (7 cases) or combined with antifungal therapy. However, conversely to literature reports in which itraconazole is the first-line therapy, voriconazole (5 cases), posaconazole, or liposomal amphotericin B (4 cases each) were mostly used in our patients.

Concerning the 23 cutaneous forms reported in the literature (described as plaques, papules, or crusted lesions; Table 2), surgical excision was performed in only 2 cases [24, 25] combined with itraconazole in a *Diaporthe* infection [24], and with amphotericin B in a *M romeroi* infection [25]. Two cases due to *Microsphaeropsis arundinis* were treated by local thermotherapy alone or associated to itraconazole [27]. The other 19 cases were treated by antifungal therapy only: itraconazole or topical clotrimazole (3 cases each), terbinafine, griseofulvin, topical miconazole or posaconazole (2 cases each), ketoconazole or amphotericin B (1 case each). Cure was obtained in 16 of 17 cases in which evolution was reported. Lesions persisted in 1 case treated topically. In our series, surgery was performed in 2 cases; voriconazole or liposomal amphotericin B were used in 2 cases.

CONCLUSIONS

In summary, whatever the species identified, coelomycetes are responsible for cutaneous and/or subcutaneous infections, which should be suspected in immunocompromised hosts harboring cutaneous plaques or nodules and originating from the tropics. After skin biopsy, a polyphasic approach combining morphological and molecular analysis is mandatory for definitive mycological identification, which should be provided by an expert laboratory. Antifungal susceptibility results vary between coelomycete genera and strains without any confirmed therapeutic relevance. Therefore, surgery should be the first-line treatment of solitary subcutaneous lesions. In case of multiple or relapsing solitary lesions, antifungal therapy (posaconazole or voriconazole) is warranted. Liposomal amphotericin B is an alternative for management of refractory cases. In SOT recipients, reduction of immunosuppression should also be considered, at least in case of multiple lesions.

Supplementary Data

Supplementary material is available online at *Open Forum Infectious* Diseases online (http://OpenForumInfectiousDiseases.oxfordjournals.org/).

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