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Dual Invasive Infection with *Phaeoacremonium parasiticum* and *Paraconiothyrium cyclothyrioides* in a Renal Transplant Recipient: Case Report and Comprehensive Review of the Literature of *Phaeoacremonium* Phaeohyphomycosis

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Despite increasing reports of human infection, data about the optimal care of *Phaeoacremonium* infections are missing. We report a case of an infection due to *Phaeoacremonium parasiticum* and *Paraconiothyrium cyclothyrioides*, initially localized to skin and soft tissue, in a kidney transplant patient. Despite surgical drainage and excision of the lesion and combination antifungal therapy with voriconazole and liposomal amphotericin B, a disseminated infection involving the lungs and brain developed and led to death. We performed a systematic literature review to assess the general features and outcome of human infections due to *Phaeoacremonium* species. Thirty-six articles were selected, and 42 patients, including ours, were reviewed. Thirty-one patients (74%) were immunocompromised because of organ or bone marrow transplantation ($n = 17$), diabetes or glucose intolerance ($n = 10$), rheumatoid arthritis or Still's disease ($n = 4$), chronic hematological diseases ($n = 3$), or chronic granulomatous disease ($n = 3$). Ten patients (24%) reported initial cutaneous trauma. Skin and soft tissue infections represented 57% of infections ($n = 24$), and disseminated infections, all occurring in immunocompromised patients, represented 14% of infections ($n = 6$). The main antifungal drugs used were azoles ($n = 41$) and amphotericin B ($n = 16$). Surgical excision or drainage was performed in 64% of cases ($n = 27$). The cure rate was 67% ($n = 28$). There were 10% cases of treatment failure or partial response ($n = 4$), 19% relapses ($n = 8$), and 7% losses to follow-up ($n = 3$). The death rate was 19% ($n = 8$). Management of *Phaeoacremonium* infections is complex because of slow laboratory identification and limited clinical data, and treatment relies on a combination of surgery and systemic antifungal therapy.

Reports of human diseases related to dark molds are increasing with the expanded spectrum of immunocompromised patients. Phaeohyphomycoses are a heterogenous group of cutaneous, subcutaneous, and systemic infections caused by fungi that are distributed worldwide, with melanized cell walls that develop in the host's tissue as dark-walled septate mycelial elements (1). *Phaeoacremonium* species, which are found in the environment in soil or in woody plants, as endophytes or as agents of plant disease, particularly in grapevines (2), are included in the phaeohyphomycosis group. Initially described in 1974 as *Phialophora parasitica* by Ajello et al. (3) and then transferred in 1996 to the new hyphomycete genus *Phaeoacremonium* by Crous et al., as *Phaeoacremonium parasiticum* (4), this fungus is a rare cause of human disease, occurring in both immunocompetent and immunosuppressed subjects. Reports of *Phaeoacremonium* infections are increasing over time, probably because laboratory confirmation of fungal pathogens has improved and because of the increase in immunocompromised conditions in the population. However, clinical and treatment data on *Phaeoacremonium* infection are scarce.

We describe a case of a disseminated infection due to *Phaeoacremonium parasiticum* and *Paraconiothyrium cyclothyrioides* in a kidney transplant recipient. We have performed a systematic review of the literature to identify clinical and mycological features and outcomes of human *Phaeoacremonium* infections.

CASE REPORT

A 71-year-old man underwent kidney transplantation in December 2011, having undergone hemodialysis for 10 years for end-stage nephroangiosclerosis.

He lived in Guadeloupe, French Caribbean, and was a retired post office employee. He reported regular gardening activity during his spare time. Several years prior to admission, he had noticed a painless, nonpruriginous nodule on the internal edge of the right middle finger. This nodule did not change over the years. No significant skin trauma was mentioned by the patient.

In December 2012, the patient was hospitalized for renal graft

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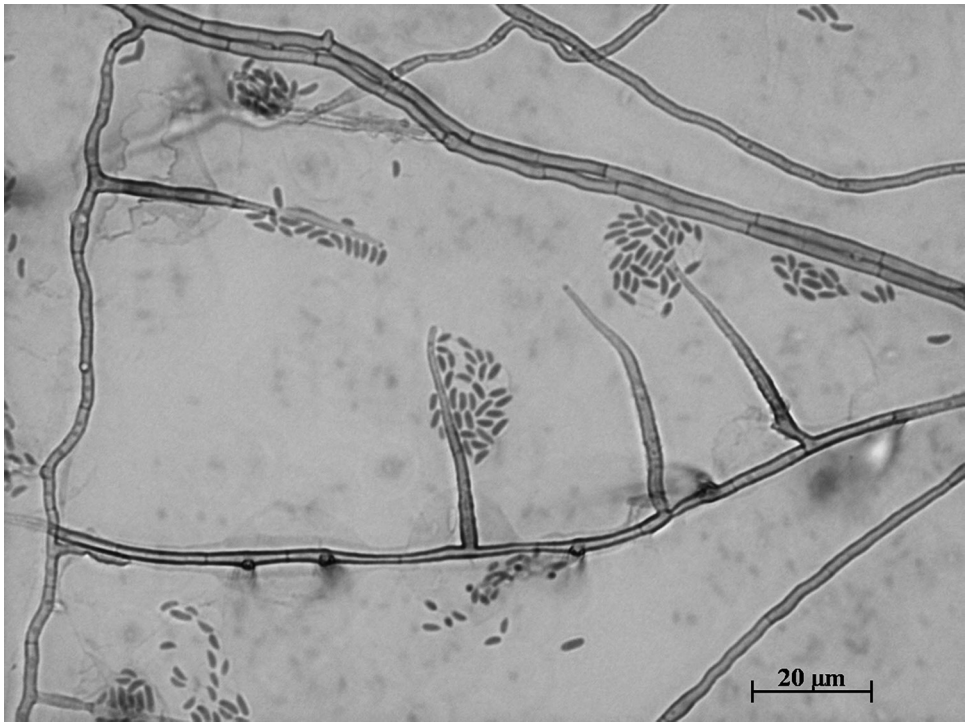

FIG 1 Microscopic features of *Phaeoacremonium parasiticum* upon culture on malt extract agar.

rejection, despite treatment with cyclosporine, azathioprine, and prednisone. The patient received a double course of plasma exchange, rituximab, and intravenous immunoglobulins before switching to another immunosuppressive regimen that included 10 mg tacrolimus twice a day (b.i.d.), 500 mg mycophenolate-mofetil b.i.d., and 10 mg prednisone daily. The hospitalization was complicated by a blood collection around the renal graft with acute anemia, requiring blood transfusion. Nine days after the second immunosuppressive course, he developed cellulitis of the right third finger, with purulent ulceration on the internal edge from the previous nodule. He had neither fever nor signs of sepsis. Surgical excision was performed in January 2013, and empirical antibiotic treatment with amoxicillin-clavulanate was given for 7 days, leading to partial relief of his symptoms. Bacterial culture of the pus was negative, and the patient was discharged on no further antibiotherapy.

Three weeks later, the patient was readmitted with renal failure requiring hemodialysis, consistent with the extensive fibrosis and tubular atrophy noted on the transplant renal biopsy specimen. There was progression of the cellulitic lesion of his right hand, despite antibiotic treatment, with extension of the swelling and the persistence of purulent discharge. Another subcutaneous lesion subsequently appeared on the posterior part of his right elbow. The patient was afebrile. He was admitted in March 2013, 7 weeks after the development of the initial purulent lesion, to the Infectious Diseases Unit (Saint-Louis Hospital, Paris, France), where new microbiological swabs were collected from both lesions, including swabs for mycological analysis.

Microscopic examination of the pus collected from the phlegmon of the third finger of the right hand revealed 45° branched septate filaments. Primary culture on malt extract agar (MEA) medium with gentamicin and chloramphenicol recovered a filamentous fungus with woolly colonies that were initially white and evolved to gray with a beige reverse (Fig. 1). Microscopic examination of the colonies identified a *Phaeoacremonium* sp., based on the presence of long and branched pigmented conidiophores, mostly monophialidic phialides, and oblong conidia. Molecular identification based on the partial sequence of the β-tubulin target gene allowed the identification of *Phaeoacremonium parasiticum* (553/557 bp; 99.6% similarity to the type strain, CBS 860.73). The MICs determined using EUCAST methodology were as follows: amphotericin B (AMB), 0.25 mg/liter; itraconazole (ITC), 2 mg/liter; voriconazole (VRC), 0.25 mg/liter; and posaconazole (PSC), 0.125 mg/liter. The minimum effective concentration (MEC) for caspofungin (CAS) was 8 mg/liter, as determined upon microscopic observation and defined as the lowest concentration of caspofungin that led to changes in mycelium architecture.

Direct microscopy of the right elbow pus revealed short, irregularly branched septate filaments harboring chlamydospores. Primary culture on MEA and Sabouraud dextrose agar (SDA) with gentamicin and chloramphenicol revealed a melanized filamentous fungus that was not microscopically identifiable due to a lack of fructification structures. Macroscopic examination after 20 days of incubation at 30°C showed the development of pycnidia (conidiomata) releasing small cylindrical conidia after 40 days of incubation (Fig. 2). Molecular identification based on the partial sequence of the β-tubulin target gene allowed the identification of *Paraconiothyrium cyclothyrioides* (463/469 bp; 98.7% similarity with the type strain, CBS 972.95). The MICs (EUCAST) were as follows: AMB, 0.25 mg/liter; ITC, 0.125 mg/liter; VRC, 0.25 mg/liter; and PSC, 0.03 mg/liter. The MEC for CAS was 4 mg/liter.

Bacterial cultures were negative. From the sole plasma sample

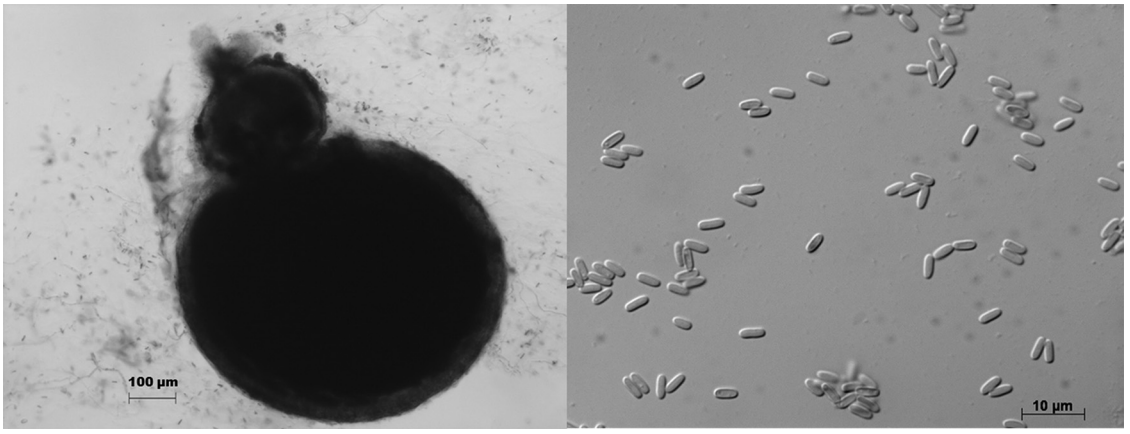

FIG 2 Microscopic features of *Paraconiothyrium cyclothyrioides* upon culture on oatmeal agar. (Left) A conidioma. (Right) Cylindrical conidia.

in which it was measured, plasma beta-(1-3)-D-glucan (Fungitell assay; Associates of Cape Cod Inc.) was detected at a level above 500 pg/ml (normal values, <80 pg/ml), whereas repeated serum galactomannan antigen testing (Platelia Aspergillus assay; Bio-Rad, Marnes-la-Coquette, France) was negative. Fungal cultures from bone marrow, blood, and sputum were negative after 3 weeks of incubation at 30°C.

A systematic screen for secondary fungal localizations was performed. Chest X-ray and a computed tomography (CT) scan showed two bilateral consolidated opacities in the upper lung lobes (Fig. 3). Cranial magnetic resonance imaging (MRI) demonstrated a focal lesion in the right parietal lobe, measuring 0.4 by 0.4 cm, with focal vasogenic edema (Fig. 4). These lesions, though asymptomatic, were both considered likely to represent fungal metastases. X-rays of the upper limbs showed no bone involvement. Echocardiography and funduscopy did not show any sign of metastatic infection.

The patient started voriconazole at 400 mg b.i.d. orally on day 1 and then at 200 mg b.i.d., and based on antifungal susceptibility testing, this was combined with liposomal amphotericin B at 3 mg/kg of body weight/day.

Antirejection drugs (tacrolimus and mycophenolate-mofetil) were stopped, and steroids were rapidly tapered to 5 mg/day but then maintained to avoid graft necrosis.

Despite low MICs of voriconazole and amphotericin B and a second surgical debridement of the right hand cellulitis, the asymptomatic pulmonary and cerebral lesions enlarged by day 20 of antifungal treatment. The patient's trough plasma voriconazole level was 6.37 mg/liter (the recommended therapeutic range is 1 to 5.5 mg/liter according to Pascual et al. [5]), and thus the dose was subsequently lowered to 150 mg b.i.d. orally to avoid toxicity.

In addition, a urinary tract infection due to *Citrobacter freundii* was diagnosed when the patient became feverish. An abdominal CT scan showed a collected mass behind the renal graft, in the right iliac fossa, corresponding to the previously known hematoma. Purulent material collected by CT-guided drainage of this collection grew *Citrobacter freundii*, and cefepime (500 mg daily) was introduced. Fungal culture of the pus was sterile. Nevertheless, despite drainage of the infected hematoma and antifungal and antibiotic therapy, the patient died of bacterial sepsis and refractory septic shock in April 2013.

MATERIALS AND METHODS

Review of the literature. We performed a systematic review of the literature by searching for articles using the following key words for the search in electronic databases: "*Phaeoacremonium*" and "phaeohyphomycosis" (MeSH key words). Relevant publications were selected using the PubMed, Embase, Google Scholar, and Cochrane databases through Jan-

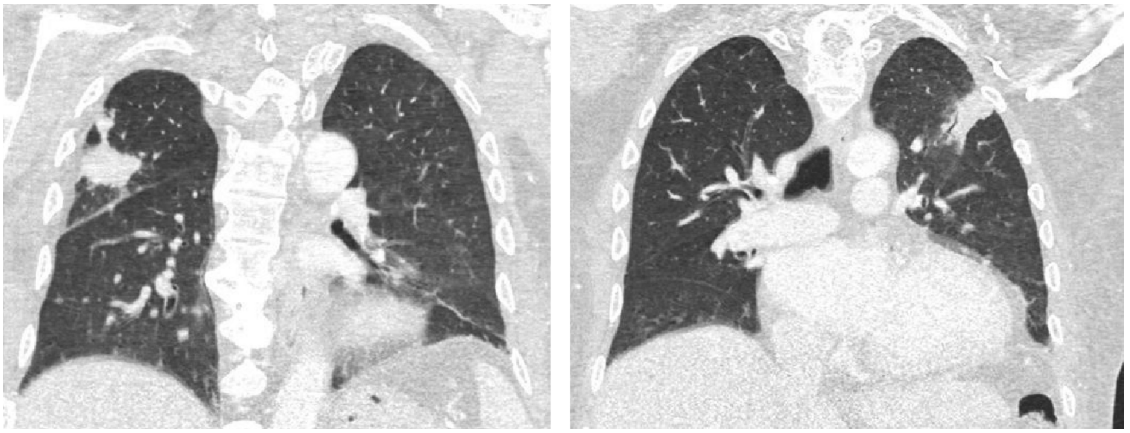

FIG 3 CT scan showing two bilateral consolidated opacities in the right (left panel) and left (right panel) upper lobes.

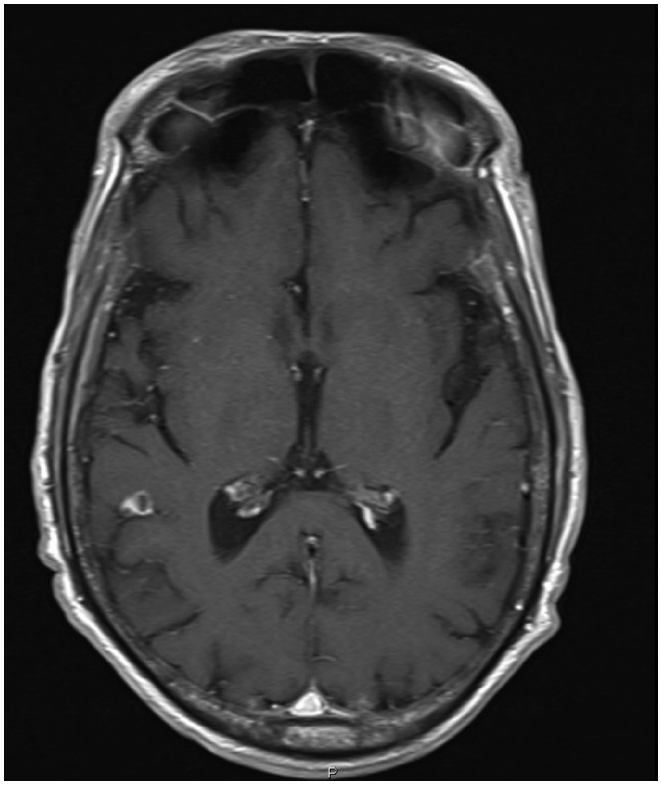

FIG 4 MRI T1 image with gadolinium showing a focal lesion in the right parietal lobe.

uary 2015. The search was completed manually using the references of the most relevant studies. Reports about *Phialophora parasitica*, the name used for *P. parasiticum* before 1996, articles which did not concern human infections or *Phaeoacremonium* species or in which mycological identification of *Phaeoacremonium* was not ensured, and articles which lacked clinical data were excluded. Patients reported more than once are presented only once. A total of 36 articles fulfilled these criteria and were included in the review, corresponding to 41 cases. All are presented, along with our case, in Table 1 (42 total cases).

RESULTS

Types of articles. Articles identified in this literature review were mostly one- or two-patient case reports. We found one series of cases of phaeohyphomycosis (6), a series of fungal lung infections in patients with chronic granulomatous disease (7), and a series of invasive fungal infections in lung transplant patients (8), as well as four brief literature reviews, each reporting a few cases of *Phaeoacremonium* infections (9–12).

Patient characteristics. More than two-thirds of patients were male (30/40 cases [75%]), with a median age of 52 years (range, 1.5 to 83 years). Only 28% of patients were over 60 years of age (11/39 patients), and most (31/42 cases [74%]) had underlying immunosuppressive medical conditions at the time when the *Phaeoacremonium* infection was diagnosed. Causes of immunosuppression were organ or bone marrow transplantation (17/31 cases [55%]), including 12 renal transplant recipients; chronic hematological diseases, such as aplastic anemia (2/31 cases [6%]) and myelodysplastic syndrome (1/31 cases [3%]); rheumatoid arthritis or Still's disease (3/31 cases [10%]); diabetes mellitus or glucose intolerance (10/31 cases [32%]); and chronic granulomatous disease (3/31 cases [10%]).

For 10 patients (10/42 patients [24%]), an initial cutaneous trauma was reported, usually several months or years earlier. Potential environmental exposure because of working or leisure activities was noted in 8 cases, including for our patient. In some cases, no trauma was noted (9).

Types of infection. As the fungus is usually acquired by traumatic inoculation from soil or by contamination with material through unnoticed skin fissures (13), infections due to *Phaeoacremonium* were mostly localized to the skin and the soft tissues (24/42 cases [57%]) and were usually only subcutaneous (21/42 cases [50%]), including 2 mycetomas and 1 onychomycosis. In three patients, skin infection secondarily extended to joints or became disseminated. In eight patients (19%), isolated osteoarticular involvement was reported (arthritis, tenosynovitis, myositis, osteomyelitis, and spondylodiscitis). In five patients (12%), isolated pulmonary infections with an appearance consistent with pulmonary nodules were reported. Airway colonization has been described (12), and a pseudo-outbreak caused by a contaminated hospital ice dispenser was reported, with *P. parasiticum* recovered from bronchoscopy specimens from 31 patients, but with no infection (14). One patient had an endophthalmitis secondary to a penetrating globe injury a few years prior.

Six patients, including ours (14%), had invasive disseminated infections associated with fungemia ($n = 3$), brain abscesses ($n = 3$), endocarditis ($n = 1$), liver and spleen abscesses ($n = 1$), and skin infectious metastasis ($n = 1$). All were immunocompromised.

Diagnosis of *Phaeoacremonium* infection. Using the European Organisation for Research and Treatment of Cancer (EORTC) criteria developed to define opportunistic invasive fungal infections in immunocompromised patients, positive cultures of *Phaeoacremonium* from sterile body sites are assumed to represent infection (15). Invasive fungal infection due to *Phaeoacremonium* is consistent on histopathological examination with the presence of hyphal elements with hematoxylin and eosin or periodic acid-Schiff stain and is more visible with Gomori methenamine silver staining, accompanied by associated inflammation and tissue damage. The combination of histopathological examination and tissue cultures is needed to establish a definitive diagnosis. A proven diagnosis of phaeohyphomycosis infection, with or without molecular identification of the *Phaeoacremonium* species, was available for 27 patients (67%), which is significantly more than the case for other invasive fungal infections, such as aspergillosis, in immunocompromised subjects, for whom possible and probable diagnoses represent almost all diagnoses (16).

Microscopic findings consist of branched, septate hyphae, simple hyphae, or hyphae occurring in strands that are smooth or verruculose to tuberculate and medium brown, becoming lighter brown to hyaline toward the conidiogenous region (2). Conidiophores are simple or branched and mostly pigmented, particularly the basal cells; phialides are aculeate, with a narrow collarette; conidia are generally allantoid, at least partly, and hyaline. Colonies on MEA are usually buff to gray-olivaceous, green-brown, or honey, rarely red, and moderately spreading and have gray to brown aerial mycelia.

The optimum temperature varies according to the *Phaeoacremonium* species, from 25 to 30°C, but *Phaeoacremonium* is also able to grow at temperatures of up to 40°C (1).

TABLE 1 Reported cases of *Phaeoacremonium* infection[a]

Reference	Patient age (yr)/sex	Underlying disease	Type of infection	Distribution of lesions	Diagnostic specimen of procedure	Species (original identification)	Surgery	Antifungal treatment[b]	Treatment duration (mo)	Evolution of disease or outcome
6	NA	Renal transplantation	SSTI	Arm	Cystic lesion	*P. inflatipes*	Yes	ITC	NA	Cured
7	17/M	Chronic granulomatous disease	Pneumonia	Lung	Lung biopsy	*P. parasiticum*	Yes	CAS/ABLC/VRC/PSC	>19	Cured
7	9/M	Chronic granulomatous disease	Pneumonia	Lung	Lung biopsy	*P. parasiticum*	No	LAMB/ABLC/VRC/PSC	>4	Cured
8	NA	Lung transplantation, rejection, diabetes	Osteomyelitis	Foot	MRI and biopsy	*P. parasiticum*	No	VRC	NA	Survived
9	31/F	Aplastic anemia	Fungemia	Blood, skin lesions	Blood cultures, skin biopsy	*P. parasiticum*	No	ABLC	NA	Died (sepsis)
9	40/M	Cardiac transplantation	SSTI	Right buttock, left forearm	Biopsy of nodular lesions	*P. parasiticum*	Yes	AMB/ITC/ABLC	12	Relapsed on ITC, died (heart disease)
10	41/M	Renal transplantation	SSTI	Right forefinger	Biopsy of nodule	*P. parasiticum*	Yes	No		Relapsed and cured by surgery
11	76/F	Still's disease	SSTI	Right leg	Biopsy of abscess	*P. rubrigenum*	Yes	ITC	3	Cured
12	26/M	Renal transplantation	Pulmonary nodules	Trachea, right lower lobe	Imaging, BAL, tracheal biopsy	*P. parasiticum*	No	ITC/VRC plus CAS	2	Partial response on VRC and CAS but then died (sepsis)
12	69/M	Diabetes	Arthritis	Right knee	Arthroscopic biopsy	*P. parasiticum*	Yes	ITC	Prolonged course	Relapsed on ITC and cured by surgery
13	49/M	Renal transplantation, diabetes	SSTI	Dorsum of left foot	Biopsy of cystic tumor	*P. parasiticum*	No	ITC plus local AMB	2	Cured
18	49/M	Renal transplantation	Brain abscess	Disseminated brain lesions	Imaging, cerebral surgical biopsy	*P. parasiticum* and *S. apiospermum*	Yes	VRC	8	Cured
19	28/M	Bone marrow transplantation	SSTI	Right arm and left knee	Biopsy of both sites	*P. venezuelense* and *Plectophomella* sp.	Yes	None	NA	LTFU
20	49/F	Renal transplantation	Pulmonary nodules	Right upper lobe	Imaging, biopsy	*Phaeoacremonium* sp.	No	PSC	4	Cured
28	56/M	Renal transplantation, diabetes	Myositis	Left thigh	Imaging	*P. parasiticum*	Yes	PSC	NA	Cured
29	61/M	Renal transplantation, redialysis, diabetes	SSTI	Right forearm	Biopsy of abscess	*Phaeoacremonium* sp.	No	LAMB	3 wk	Cured but died from pneumonia
46	45/M	Liver transplantation	SSTI plus endocarditis	Interdigital space, blood	Blood cultures, valvular vegetations	*P. parasiticum*	No	AMB/FLC/AMB plus ITC	3	Died (disseminated infection)
47	1.5/M	Aplastic anemia	Fungemia	Blood, spleen, liver	Blood and bone marrow cultures	*P. inflatipes*	No	AMB	1	Died (septic shock)
48	24/M	Chronic granulomatous disease	Disseminated	Upper lung, temporal lobe	Imaging, cerebral biopsy	*P. parasiticum*	No	CAS plus LAMB/VRC plus TER	1.5	Died (fungal ventriculitis)
49	74/M	Lung transplantation	Pulmonary nodules	Bilateral lungs	Imaging, no differential diagnosis	*P. parasiticum*	No	VRC	3	Cured
50	52/M	Glucose intolerance	Spondylodiscitis	Cervical spine	Imaging	*P. venezuelense*	No	AMB/VRC	6	Cured
51	59/F	None	SSTI	Right knee	Biopsy of cystic lesion	*P. parasiticum*	Yes	None		Cured
52	26/F	None	SSTI	Left forearm	Biopsy of lesion	*P. parasiticum*	Yes	AMB/ITC	2	Cured
53	30/M	NA	SSTI	Left foot	Biopsy of foot mass	*P. inflatipes*	Yes	AMB/ITC	2.5	Cured
54	61/F	Rheumatoid arthritis, hemodialysis	SSTI	Left foot	Biopsy of subcutaneous tumor	*P. griseorubrum* (*P. rubrigenum*)	Yes (3)	ITC/FLC	5	Relapsed on ITC and then on FLC
55	55/M	Renal transplantation	SSTI	Left foot and ankle	Biopsy of nodules	*P. parasiticum* (*P. rubrigenum*)	Yes (2)	ITC/ITC plus TER/FLC	>11	Relapsed on ITC and then on ITC plus TER, failure on FLC
55	19/M	None	SSTI	Left ankle	Biopsy of nodule	*P. alvesii* (*P. aleophilum*)	Yes	ITC	2	Relapsed 6 times with surgery alone, cured with ITC and surgery
56	61/M	Renal transplantation, diabetes	SSTI	Right middle finger	Extended swelling	*P. aleophilum*	No	ABLC/VRC	1.5	Cured

57	54/M	Renal transplantation, diabetes	SSTI	Right middle finger	Biopsy of large mass	*P. aleophilum*	Yes	FLC plus AMB	2 days	Cured
58	74/M	Rheumatoid arthritis	SSTI	Left leg	Biopsy of a crusted nodule	*Phaeoacremonium* sp.	Yes	ITC	23	Cured
59	NA/M	Rheumatoid arthritis and vasculitis	SSTI	Dorsum of hand	Biopsy of nodule	*P. parasiticum*	Yes	None/VRC	6	Relapsed after surgery alone and cured with VRC and surgery
59	57/M	Diabetes	Arthritis	Left knee	X-ray and MRI	*P. parasiticum*	No	FLC/ITC/AMB/LAMB/VRC	More than 7	Cured
60	66/M	None	SSTI	Ankle	Needle puncture	*P. inflatipes*	Yes	None	NA	Cured
61	83/F	None	SSTI and arthritis	Left foot and knee	Biopsy of foot mass	*P. alvesii* (*P. inflatipes*)	Yes	None	NA	Cured
62	14/F	None	Arthritis	Right knee	Imaging	*Phaeoacremonium* sp.	Yes	VRC	12	Cured
63	66/M	Coronary disease	Tenosynovitis	Left middle finger	Imaging	*Phaeoacremonium* sp.	Yes	ITC	3	Relapse after surgery on ITC consistent with tendon rupture, cured by another surgery
64	54/F	Myelodysplasia and IgA deficiency	Osteomyelitis and bursitis	Right olecranon	X-ray, bone erosion, puncture	*Phaeoacremonium* sp.	Yes	ITC	Quickly stopped because of side effects	Cured
65	52/F	Diabetes	Mycetoma	Right foot	MRI, biopsy of nodules	*P. parasiticum*	Yes	ITC/AMB/ITC	>24	Partial response after five surgical procedures and prolonged course of ITC
66	41/M	NA	Mycetoma	Right foot	Biopsy of sinuses	*P. krajdenii*	No	ITC	4	LTFU
67	55/M	None	Onychomycosis	Right big toenail	Nail biopsy	*P. parasiticum*	Yes	Topical sulconazole	2	Cured
68	19/M	None	Endophthalmitis	Left eye	Vitreous biopsy	*P. parasiticum*	Yes	VRC plus local AMB	2	Partial response on VRC, LTFU
Our case	70/M	Renal transplantation	SSTI and then disseminated	Pulmonary upper lobes, parietal lobe	Imaging, subcutaneous biopsy	*P. parasiticum* and *P. cyclothyrioides*	Yes	VRC/VRC plus LAMB	1	Died (sepsis)

[a] Abbreviations: ABLC, amphotericin B lipid complex; AMB, amphotericin B; BAL, bronchoalveolar lavage; CAS, caspofungin; F, female; FLC, fluconazole; ITC, itraconazole; LAMB, liposomal amphotericin B; LTFU, lost to follow-up; M, male; NA, not available; PSC, posaconazole; SSTI, skin and soft tissue infection; TER, terbinafine; VRC, voriconazole.

[b] Successive courses are indicated by slashes.

Identification of *Phaeoacremonium* species is difficult because the cultural and microscopic distinguishing characteristics are relatively minor (2). Also, some of the most common species causing human disease were not described before 2005 (or taxonomically redressed since then) and therefore were probably misidentified in earlier publications (9). Molecular methods have been developed to confirm species identifications (17); these are best supported by phylogenetic analyses of actin, β-tubulin, and calmodulin gene sequences. Mostert et al. developed a multiple-character electronic identification key to facilitate routine species identification based on micromorphological characters, such as conidiophore morphology, phialide type and morphology, conidial size and shape, and cultural characters, such as colony color on MEA, yellow pigment production on potato dextrose agar (PDA), growth rate at 25°C, and maximal growth temperature, in addition to phylogenetic analyses of selected regions of the β-tubulin gene (2). Using this identification key, four strains of *Phaeoacremonium* in our review were reidentified *a posteriori* (2). In our case, the culture sample was sent to the National Reference Laboratory (Institut Pasteur, Paris, France) to confirm the species identification by polyphasic identification.

Eight different *Phaeoacremonium* species causing human infections were recorded. The most frequent species identified in human infections were *P. parasiticum*, *P. inflatipes*, and *P. rubrigenum*, but emerging species, such as *P. aleophilum* and *P. venezuelense*, have been described since 2005 (1, 2). *Phaeoacremonium parasiticum* was the most prevalent species, causing 23 cases of infection (55%). Other species identified in this review were three cases of *P. inflatipes*, two cases each of *P. alvesii* and *P. venezuelense*, and one case each of *P. aleophilum*, *P. griseorubrum*, *P. krajdenii*, and *P. rubrigenum*. In six cases, species identification was not available. However, misidentification of *Phaeoacremonium* species could have occurred, as molecular diagnosis was available for only 38% of cases (16/42 cases), in addition to standard microscopic identification from fungal cultures. In four cases, the *Phaeoacremonium* species identification was retrospectively modified using molecular diagnosis after the initial microscopic diagnosis—former descriptions of *P. rubrigenum*, *P. aleophilum*, and *P. inflatipes* were changed to *P. griseorubrum*, *P. parasiticum*, and *P. alvesii*, respectively (2).

For three patients, including our patient, a second fungus was identified contemporaneously. One patient had a brain abscess due to *P. parasiticum* and *Scedosporium apiospermum* (18). The second had a subcutaneous infection, with different samples growing *P. venezuelense* and *Plectophomella* sp. (19). In our patient, *P. cyclothyrioides* was isolated in addition to *P. parasiticum*. All three patients were immunocompromised. In one case of *Phaeoacremonium* lung infection, another dematiaceous fungus (*Dactylaria constricta*) was isolated from bronchial fluid but not from the lung biopsy specimen and was assumed to be a colonizer of the respiratory tract rather than a pathogen (20).

Treatment. There is no standard treatment for phaeohyphomycosis (21). The reported systemic antifungal agents used to treat *Phaeoacremonium* phaeohyphomycosis included amphotericin B in deoxycholate or lipid form, azoles (voriconazole, itraconazole, fluconazole, and posaconazole), terbinafine, and caspofungin, but the optimal antifungal treatment for invasive disease is uncertain. *In vitro*, *Phaeoacremonium* is usually susceptible to azoles, particularly voriconazole, and to amphotericin B (9, 22), but reduced amphotericin B and itraconazole sensitivities have been described (23, 24). In a large literature review of *in vitro* antifungal activities for reference antifungal agents on various fungi (23), MIC ranges for 18 isolates of *P. parasiticum* were 0.125 to 2 mg/liter for voriconazole, 0.125 to 16 mg/liter for amphotericin B, and 0.25 to 32 mg/liter for itraconazole. These are consistent with previous data (24). However, *Phaeoacremonium* sp. *in vitro* susceptibility testing against antifungal drugs is not standardized, and methods for MIC determination and breakpoints still need to be established (9).

Recent European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and European Confederation of Medical Mycology (ECMM) guidelines concerning phaeohyphomycosis proposed voriconazole for the treatment of central nervous system phaeohyphomycosis because of its ability to achieve adequate cerebrospinal fluid levels (25). Combination antifungal therapy is recommended in general for systemic phaeohyphomycosis, for cerebral abscesses when surgery is not possible, and for disseminated infections in immunocompromised patients (25), but there are neither data nor specific recommendations for *Phaeoacremonium* infections in these settings. There are also no data about the optimal dosing, treatment duration, and resistance management. Experts recommend a prolonged duration of therapy, ranging from weeks to months (25).

Overall, 86% of patients (36/42 patients) received systemic antifungal therapy. Different classes of antifungal drugs were used for the treatment of *Phaeoacremonium* phaeohyphomycosis. Azoles (41 prescriptions) were usually prescribed, including itraconazole ($n = 18$), voriconazole ($n = 14$), fluconazole ($n = 5$), and posaconazole ($n = 4$). Amphotericin B was used in 16 patients (38%), including liposomal amphotericin B ($n = 5$) and amphotericin B lipid complex ($n = 5$). Other antifungal systemic therapies were caspofungin ($n = 3$) and terbinafine ($n = 2$). Combinations of antifungal drugs and sequential therapies because of side effects, failure, or relapse were prescribed for 17% (6/36 patients) and 39% (14/36 patients) of treated patients, respectively.

Antifungal susceptibility testing was mentioned for nine patients, and MICs (or MECs) were specified in eight cases (Table 2). The lowest MICs were seen with the extended-spectrum triazoles voriconazole and posaconazole. In contrast, MICs of fluconazole and flucytosine were high, ranging from 8 to 64 mg/liter.

The mean duration of systemic antifungal treatment was 3 months (range, 0.06 to 24 months) in the evaluable reports. Topical antifungal agents were used on three patients, in addition to surgical treatment and/or systemic antifungal drugs.

In addition, similarly to other invasive fungal infections (26), surgical resection should be considered for *Phaeoacremonium* phaeohyphomycosis to reduce the infectious inoculum size, particularly in brain abscesses. Resection of infected lesions permits the elimination of areas containing viable fungi in necrotic tissue or sites where antifungal drug penetration is low. Moreover, for subcutaneous and localized *Phaeoacremonium* infections, wide-excision surgery appears to be the main treatment option to avoid relapses and may be used alone to cure localized infections in immunocompetent subjects (9, 10).

Twenty-seven patients (64%) underwent surgical excision or drainage of the lesions, among whom 26 had localized infections. Among them, 14% of patients (6/42 patients) received no systemic antifungal therapy and were successfully cured by surgery alone. Ten patients underwent multiple surgical interventions (range, 2 to 7), and one underwent drainage of brain abscesses.

TABLE 2 Antifungal susceptibilities of reported isolates of *Phaeoacremonium* spp.

Reference	MIC or MEC (mg/liter) at indicated time(s) (h)[a]							
	AMB	ITC	VRC	PSC	FLC	CAS	TER	5FC
9	0.5/2 (48/72)	1/8 (48/72)	0.125/0.125 (48/72)	0.25/0.25 (48/72)	NA	NA	NA	NA
9	1/2 (48/72)	0.03/0.125 (48/72)	0.03/0.06 (48/72)	0.03/0.03 (48/72)	NA	NA	NA	NA
47	0.75	NA	NA	NA	NA	NA	NA	NA
48	2 (24)	NA	0.25 (24)	0.5 (24)	NA	>8 (24)	0.5 (24)	NA
55	2 (72)	>16 (72)	1 (72)	NA	8 (72)	NA	2 (72)	NA
55	2 (72)	8 (72)	1 (72)	NA	8 (72)	NA	2 (72)	NA
68	0.25	1	0.06	NA	64	NA	NA	64
This study	0.25	2	0.25	0.125	NA	8	NA	NA

[a] All data except those for CAS are MICs. Data for CAS are MECs. AMB, amphotericin B; ITC, itraconazole; VRC, voriconazole; PSC, posaconazole; FLC, fluconazole; CAS, caspofungin; TER, terbinafine; 5FC, 5-fluorocytosine; NA, not available.

Among the patients who were immunocompromised, a reduction of the immunosuppressive therapy in order to improve the immune response against infection and/or to prevent drug-induced toxicity was mentioned in five cases, including our patient, for whom surgical removal of the transplanted kidney was planned to allow the cessation of prednisone, but unfortunately, he died before surgery.

Outcomes. The follow-up duration was variable, with a median time of 12 months (range, 2 to 72 months), and it was unavailable for many (21/42 patients [50%]) patients. Overall, 28 patients (67%) were completely cured after treatment. Partial responses or failures were described for four patients (10%), and relapses for eight (19%). The number of relapses was variable (range, 1 to 6). Three patients (7%) were lost to follow-up.

Eight patients (19%) died, either related directly to the fungal infection ($n = 2$), related to preexisting medical conditions ($n = 1$), or related to another sepsis complication ($n = 5$). The median time between diagnosis and death due to infection was 60 days (range, 30 to 386 days). All of these patients were immunocompromised.

No death related to fungal infection was reported for those with localized infections.

DISCUSSION

Among the 42 different species of *Phaeoacremonium* already described (27), less than a fourth were involved in human infections, and the most frequent species identified in human infections was *P. parasiticum*, as in our report patient.

As environmental exposition and/or trauma was often reported prior to the infection, these infections were mainly subcutaneous and predominated in lower limbs. In solid organ transplant recipients, similarly to our report, infections due to dematiaceous fungi occur late and present most frequently as skin or soft tissue infections with an indolent course and delayed diagnosis (28), varying from 2 months to 14 years after transplantation, with the fungal lesion evolving over weeks to years before the microbiological diagnosis is made. Our patient developed a subcutaneous nodule of the finger many years ago that remained stable over time. We assumed that this nodule was a chronic localization of *P. parasiticum* probably contracted during his gardening activity, from which an invasive extension to soft tissue occurred following an increase in immunosuppressive therapy, a time when disseminated infections mainly concern immunocompromised subjects, such as organ transplant patients, and are associated with a poor prognosis (9).

We observed a high plasma level of (1-3)-β-D-glucan in our patient, whereas he had no clinical signs of disseminated infection. The (1-3)-β-D-glucan is a polysaccharide component of the cell walls of most fungi, and its measurement in plasma offers a noninvasive method for the surveillance and diagnosis of invasive fungal infections. To our knowledge, elevated levels of (1-3)-β-D-glucan have been reported only once for *Phaeoacremonium* infections (29), but with a low level compared to our case, and have never been described for *Paraconiothyrium* infections. We suggest that detection of serum (1-3)-β-D-glucan could be added to the management of *Phaeoacremonium* phaeohyphomycosis if a disseminated infection is suspected and/or for immunocompromised subjects. Ben-Ami et al. suggested a possible cross-reactivity of galactomannan-directed antibodies with dematiaceous molds, but there are no data concerning *Phaeoacremonium* (30). It should be noted that, in our case, the serum was negative for the galactomannan antigen.

Interestingly, in three patients, including ours, concomitant dual fungal infections were reported, involving *Scedosporium apiospermum*, *Plectophomella* sp., and *Paraconiothyrium cyclothyrioides*. Although infections by more than one fungus are not rare in immunocompromised patients (31–33), even by two species of the same genus (34) or by different serotypes of the same species (35), it is not easy to identify mixtures (19). Moreover, reports of mixed dematiaceous infections are scarce (36, 37). These data underline the need to ideally obtain tissue samples from involved organs to improve diagnosis and treatment. In our case, it was difficult to assess which fungus caused disseminated disease, in the absence of cerebral or pulmonary specimens and because of the adverse evolution of our patient's illness. We believe that *Paraconiothyrium cyclothyrioides*, which was also isolated from the pus of the left elbow lesion, may have been an aggravating factor. Nevertheless, because the optimum growth temperature for *P. cyclothyrioides* ranges from 27°C to 33°C (38), it is less likely that this fungus was involved in the disseminated lesions. *Paraconiothyrium cyclothyrioides* is a coelomycete found in the soil and has been reported in only two human infections (39, 40). In these reports, both patients were organ transplant recipients (kidney and liver) and had chronic skin lesions of the lower extremities. In one for whom the information was provided, posaconazole led to a complete resolution of the lesions (39). Other reports of *Paraconiothyrium* infection in humans involved *P. maculicutis* (41) and a *Paraconiothyrium* sp. (42), also in immunocompromised individuals with chronic skin lesions, while coelomycetes in general have been

associated with subcutaneous infection (43), deep-seated infection (44), and disseminated infection (45) in immunocompromised patients.

In conclusion, we present a case of a fatal disseminated infection due to *Phaeoacremonium parasiticum* and *Paraconiothyrium cyclothyrioides* in a renal transplant recipient. A literature review emphasizes the fact that environmental exposure and comorbidities are important in *Phaeoacremonium* infection physiopathology, that appropriate identification may be difficult, and that optimal treatment should combine surgery and antifungal agents.

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