Treatment of subcutaneous phaeohyphomycosis and prospective follow-up of 17 kidney transplant recipients

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Background: Subcutaneous phaeohyphomycosis in solid organ recipients may have an adverse outcome.

Objective: We sought to describe the disease course, treatment, and outcome of allograft function in kidney transplant recipients with phaeohyphomycosis.

Methods: Seventeen patients were followed for a mean period of 25.4 months to analyze the clinical response to treatment.

Results: There was no treatment failure or relapsing disease among 12 patients who completed treatment. Two patients were still in treatment with disease remission. One patient discontinued the study during treatment with partial remission, one died after finishing treatment with disease remission, and one was dropped from the study because contact was lost. Immunosuppressive regimens were not changed. Two of 17 patients had a significant reduction in allograft function.

Limitations: The follow-up time was short and the number of patients was small.

Conclusions: The outcome of phaeohyphomycosis in kidney transplant recipients was favorable with minimal impact on renal allograft function. (J Am Acad Dermatol 2009;61:977-85.)

Key words: dematiaceous; dermatomycoses; immunosuppression; itraconazole; kidney transplantation; opportunistic infections; phaeohyphomycosis.

Kidney transplantation is considered the best option for renal replacement therapy. Although maintenance immunosuppression is required for long-term graft survival free of rejection episodes, kidney transplant recipients are at a high risk for opportunistic infections.1 Fungal infection of superficial skin and subcutaneous tissues is common mainly during the maintenance phase of immunosuppressive treatment.2 Phaeohyphomycosis is an emerging mycosis that has been reported in solid organ transplant recipients; it is caused by a variety of fungal species, most of which are considered opportunistic pathogens.3 A distinctive characteristic of this group of pathogens is the melanin pigmentation presented in their cell wall which is responsible for the generic and widely used term “dematiaceous” or “pigmented filamentous fungi.”4 Phaeohyphomycosis exhibits a variety of clinical presentations, ranging from keratitis and solitary subcutaneous nodules to fulminant and rapidly fatal disseminated disease.5,6 This is a prospective report of treatment and the clinical outcomes of 17 kidney transplant recipients with subcutaneous phaeohyphomycosis.
METHODS

Study design

The study was approved by our institutional review board. Patients who had a kidney allograft and a suspicion of dermatologic disease were continuously referred by the division of nephrology to the department of dermatology from January 2000 to December 2007.

The study population consisted of 17 consecutive, prospectively identified kidney transplant recipients with subcutaneous dematiaceous fungal infection. Information was obtained from each patient's chart about age, sex, date of transplantation, type of kidney donor, type of primary immunosuppression, serum creatinine level, and previous episodes of minor trauma with skin injury.

The time after transplantation to diagnosis was defined as the time period between the transplantation date and the documented phaeohyphomycosis. Time of follow-up was defined as the time between the first and the most recent visit to the dermatology outpatient center before July 2008.

The clinical care of the patients and the immunosuppressive regimens were in accordance with institutional standards.5

Diagnosis

Subcutaneous fungal infection was suspected when single or multiple subcutaneous cysts were present with no evidence of inflammation in the surrounding skin areas. The subcutaneous cysts were assessed by physical examination and their presence and anatomic characteristics were confirmed by ultrasonographic examination when appropriate. A tissue biopsy of the subcutaneous cyst was performed in all patients. Subcutaneous lesions presented as verrucous, infiltrating, or vegetating plaques were also considered highly suspicious for fungal infection and were biopsied as well. Proven dematiaceous fungal infection was defined as: (1) a histopathological examination that revealed tissue invasion by a dark-pigmented fungus; (2) a negative histopathological examination with a tissue culture result positive for a dematiaceous fungus; or (3) positive culture of sample obtained by sterile needle aspiration. Light microscopic examinations were performed on tissue slides stained according to hematoxylin-eosin, Grocott-Gomori, and melanin-specific Fontana-Masson standard methods. Cultures were performed on Sabouraud glucose agar and potato dextrose agar at 25°C to 30°C.

Capsule Summary

- Phaeohyphomycosis is an opportunistic infection that may have an adverse outcome with fatal disseminated disease in immunocompromised hosts such as kidney transplant recipients.
- Surgical excision of the lesions in combination with itraconazole for at least 6 months is an effective treatment for subcutaneous phaeohyphomycosis in these patients.
- Calcineurin inhibitor immunosuppressive drugs may exert a protective effect against life-threatening invasive disease.
- The impact of phaeohyphomycosis on renal allograft function is minimal.

Treatment

Treatment for the subcutaneous dematiaceous fungal infection consisted of surgical excision of the lesions in combination with antifungal therapy or surgical excision alone in selected cases. Partial surgical excision was defined as a situation where it was not possible for the surgeon to safely remove the entire lesion because of its extension or proximity to anatomically essential structures.

A systemic azole antifungal agent was then initiated. Patients given complementary antifungal therapy belonged to one of 3 categories: (1) patients with multiple lesions in different body sites, which can be indicative of hematogenic dissemination; (2) those with lesions that were not susceptible to complete surgical removal; and (3) those in whom a fungus with documented neurotropism was isolated. All patients with relapsing disease, treatment failure, or a de novo dematiaceous fungal infection were also given antifungal therapy. Systemic itraconazole was the preferred choice. The initial prescribed dose ranged from 100 to 800 mg/d based on the severity of the infection and was further adjusted according to the clinical response and the occurrence of hepatic toxicity. Fluconazole, terbinafine, and conventional amphotericin B also were allowed when an individual patient presented severe disease, a poor response to itraconazole, or hepatic toxicity that did not reverse after itraconazole dose reduction. The duration of antifungal therapy was based on the clinical response. A 6-month period of disease remission was required for termination of antifungal therapy. As azoles are metabolized and inhibit the hepatic cytochrome P450 enzymatic system (mainly CYP2C9, CYP2C19, and CYP3A4),7 the serum levels of calcineurin inhibitors, also metabolized by these enzymes, were closely monitored.
Outcome measurements

The disease course and response to therapy was determined by comparing the clinical presentation at first and last visit. Complete disease remission or cure was defined as the absence of documented phaeohyphomycosis lesions during or after a treatment course. Partial remission was defined as the improvement in the number or dimension of the documented phaeohyphomycosis lesions during a treatment course. Relapse was defined as the occurrence of new phaeohyphomycosis lesions in a patient previously considered to be in remission at least 6 months after finishing a full treatment course. Treatment failure was defined as the documented occurrence of new phaeohyphomycosis lesions less than 6 months after finishing a complete treatment course. The occurrence of new phaeohyphomycosis lesions caused by a different fungus species after a complete treatment course and disease remission was defined as de novo disease.

Serum creatinine levels were used as an indicator of renal allograft function. The impact of dematiaceous fungal infection and its specific treatment on renal allograft function was assessed by measuring the difference between the serum creatinine level before initiation of treatment (before-treatment creatinine) compared with levels after finishing the prescribed phaeohyphomycosis treatment (after-treatment creatinine). For those patients still receiving antifungal therapy at the end of the follow-up period, the serum creatinine level at the last outpatient visit was used as the after-treatment creatinine value. Renal allograft function was considered stable or unchanged if the serum creatinine level was lower, equivalent, or displayed a nonsignificant increase at the end of the treatment course. A nonsignificant increase in the serum creatinine level was defined as a less than 20% increase in the after-treatment creatinine as compared with the before-treatment measurement.

RESULTS

Demographic data and immunosuppression

Of 3885 patients who received a kidney allograft at our institution during the study period, 1243 (31.9%) had a dermatologic disease. Subcutaneous fungal infection caused by a dematiaceous filamentous fungi was present in 17 patients (1.4%; 12 male, 70.6%), with a mean age of 52.4 ± 7.8 years. The demographic characteristics of these patients are presented in Table I. The male:female ratio was 2.4:1. The onset of clinical phaeohyphomycosis ranged from 4 to 144 months after transplantation. The majority of patients (52.9%) received a graft from a deceased donor. No patient had minor trauma with skin injury.

Table I. Demographic characteristics and immunosuppression of kidney transplant recipients with subcutaneous phaeohyphomycosis

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>52.4 ± 7.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>12</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
</tr>
<tr>
<td>Time after transplantation to diagnosis (mo)</td>
<td>26</td>
</tr>
<tr>
<td>Donor source</td>
<td></td>
</tr>
<tr>
<td>Living</td>
<td>8</td>
</tr>
<tr>
<td>Deceased</td>
<td>9</td>
</tr>
<tr>
<td>Minor trauma with skin injury</td>
<td>0</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td></td>
</tr>
<tr>
<td>PRED AZA CSA</td>
<td>3</td>
</tr>
<tr>
<td>PRED AZA TAC</td>
<td>4</td>
</tr>
<tr>
<td>PRED MMF TAC</td>
<td>6</td>
</tr>
<tr>
<td>PRED CSA</td>
<td>3</td>
</tr>
<tr>
<td>PRED TAC</td>
<td>1</td>
</tr>
</tbody>
</table>

AZA, Azathioprine; CSA, cyclosporine; MMF, mycophenolic acid mofetil; PRED, prednisone; TAC, tacrolimus.

Immunosuppression regimens at the time of transplantation were distributed as follows: 17.6% received prednisone (PRED)/azathioprine/cyclosporine, 23.5% PRED/azathioprine/tacrolimus, 35.3% PRED/mycophenolic acid mofetil/tacrolimus, 17.6% PRED/ cyclosporine, and 6.0% PRED/tacrolimus (Table I).

Clinical presentation

Phaeohyphomycotic-specific subcutaneous lesions were observed only in distal body areas (Table II). Twelve patients (70.6%) presented with a single lesion. A representative single cyst is shown in Fig 1, A. A total of 5 patients (29.4%) presented with more than one lesion and two patients (11.8%) presented with more than 2 to 3 lesions (Fig 1, B). Less common clinical manifestations included one verrucous plaque on the ankle of a patient (5.9%) (Fig 1, C), one infiltrating plaque on the arm of a patient (5.9%), one vegetating plaque on the leg of a patient (5.9%), and infiltrating plaques on both legs of a patient (5.9%). Systemic disease was not observed.

The most frequent sites of involvement were the legs and feet, each in 5 patients (29.4%). Other sites with lesions were arms and hands, in two patients each (11.8%), and on the heel of one patient (5.9%). Two patients (11.8%) presented lesions on distinct sites. Patient 9 had one infiltrating plaque on the antecubital fossa of the right arm and later, after starting antifungal therapy, a phaeohyphomycotic cyst positive for the same agent was observed on each one of his legs. Patient 16 had multiple cysts and an infiltrating plaque on each one of his legs. No
patient experienced painful or swollen cysts, inflammation in the surrounding skin areas, or regional or systemic lymphadenopathy.

**Histology**

Histologically, granulomatous inflammation with a variable neutrophilic infiltrate and central abscess formation were commonly observed (Fig 2, A). Characteristic yellow-brown pigmented fungal hyphae within the granulomatous inflammation were present in 16 patients (94.1%) (Fig 2). No fungal hyphae were noted outside the cyst wall or beyond the extension of deep tissue-infiltrating plaques.

**Mycology**

A total of 9 species of fungi were isolated. *Exophiala* species accounted for two patients (11.8%), *Cladosporium* species for one (5.9%), *Phialophora richardiae* for one (5.9%), *Fonsecaea pedrosoi* for one (5.9%), *Phaeoacremonium inflatipes* for one (5.9%), *Scedosporium apiospermum* for one (5.9%), and *Cochliobolus australiensis* for one (5.9%). Of interest, one patient was infected by two different fungus species (patient 10). After treatment, this patient developed a second infection with a different fungus species on the primary infection site. The initial infection was a cyst on the back of the right hand positive for *Alternaria alternata*. Twelve months after finishing the first prescribed treatment, he presented with another cyst that was positive for *Colletotrichum gloeosporioides* at the same site. Unidentified species of dematiaceous fungi were found in 4 patients and 4 patients were negative for dematiaceous fungi in culture (Table II).

**Prescribed treatment**

Complete surgical excision was performed in 12 patients (70.6%). Partial surgical excision was performed in 4 patients (23.5%, patients 3, 9, 12, and 16) because of the multiplicity and extent of the lesions. One patient (patient 15) showed a complete spontaneous remission after cystic needle aspiration and no additional treatment was necessary. Systemic antifungal therapy was prescribed to 12 patients (70.6%). The most frequently used drug was itraconazole, which was administered to 11 (91.6%) of 12 patients who received antifungal therapy. Fluconazole was administered to one patient (8.3%, patient 5) and terbinafine in combination with itraconazole to one patient (8.3%, patient 9) with severe disease. Conventional amphotericin B was administered to two patients (11.8%, patients 9 and 16) because of severe disease and to one patient (5.9%, patient 12) because of itraconazole-related hepatic toxicity (Table II). The mean duration of antifungal therapy

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**Table II. Clinical presentation, pathological data, and treatment of subcutaneous phaeohyphomycosis in kidney transplant recipients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Body location</th>
<th>Type of lesions</th>
<th>No. of lesions</th>
<th>Culture result</th>
<th>Surgical therapy</th>
<th>Antifungal therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Finger</td>
<td>Cyst</td>
<td>Single</td>
<td><em>Exophiala</em> species</td>
<td>C</td>
<td>ITRA</td>
</tr>
<tr>
<td>2</td>
<td>Heel</td>
<td>Cyst</td>
<td>Single</td>
<td><em>Cladosporium</em> species</td>
<td>C</td>
<td>ITRA</td>
</tr>
<tr>
<td>3</td>
<td>Foot</td>
<td>Cyst</td>
<td>Multiple</td>
<td><em>Exophiala</em> species</td>
<td>P</td>
<td>ITRA</td>
</tr>
<tr>
<td>4</td>
<td>Leg</td>
<td>Cyst</td>
<td>Single</td>
<td>Negative</td>
<td>C</td>
<td>ITRA</td>
</tr>
<tr>
<td>5</td>
<td>Foot</td>
<td>Cyst</td>
<td>Single</td>
<td>Negative</td>
<td>C</td>
<td>FLUC</td>
</tr>
<tr>
<td>6</td>
<td>Foot</td>
<td>Cyst</td>
<td>Single</td>
<td><em>Phialophora richardiae</em></td>
<td>C</td>
<td>ITRA</td>
</tr>
<tr>
<td>7</td>
<td>Ankle</td>
<td>Plaque</td>
<td>Single</td>
<td>Negative</td>
<td>C</td>
<td>ITRA</td>
</tr>
<tr>
<td>8</td>
<td>Leg</td>
<td>Cyst</td>
<td>2</td>
<td>Negative</td>
<td>C</td>
<td>ITRA</td>
</tr>
<tr>
<td>9</td>
<td>Arm and legs</td>
<td>Cyst and plaque</td>
<td>3</td>
<td><em>Fonsecaea pedrosoi</em></td>
<td>P</td>
<td>ITRA/TERB/AMB</td>
</tr>
<tr>
<td>10</td>
<td>Hand</td>
<td>Cyst</td>
<td>2</td>
<td><em>Alternaria alternata</em> and <em>Colletotrichum gloeosporioides</em></td>
<td>C</td>
<td>None</td>
</tr>
<tr>
<td>11</td>
<td>Arm</td>
<td>Cyst</td>
<td>Single</td>
<td><em>Phaeoacremonium inflatipes</em></td>
<td>C</td>
<td>ITRA</td>
</tr>
<tr>
<td>12</td>
<td>Leg</td>
<td>Plaque</td>
<td>Single</td>
<td>Dematiaceous fungus</td>
<td>P</td>
<td>ITRA/AMB</td>
</tr>
<tr>
<td>13</td>
<td>Leg</td>
<td>Cyst</td>
<td>Single</td>
<td><em>Scedosporium apiospermum</em></td>
<td>C</td>
<td>None</td>
</tr>
<tr>
<td>14</td>
<td>Foot</td>
<td>Cyst</td>
<td>Single</td>
<td>Dematiaceous fungus</td>
<td>C</td>
<td>None</td>
</tr>
<tr>
<td>15</td>
<td>Arm</td>
<td>Cyst</td>
<td>Single</td>
<td>Dematiaceous fungus</td>
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<td>None</td>
</tr>
<tr>
<td>16</td>
<td>Legs</td>
<td>Cyst and plaque</td>
<td>Multiple</td>
<td>Dematiaceous fungus</td>
<td>P</td>
<td>ITRA/AMB</td>
</tr>
<tr>
<td>17</td>
<td>Leg</td>
<td>Cyst</td>
<td>Single</td>
<td><em>Cochliobolus australiensis</em></td>
<td>C</td>
<td>None</td>
</tr>
</tbody>
</table>

*AMB*, Conventional amphotericin B; *C*, complete; *FLUC*, fluconazole; *ITRA*, itraconazole; *NA*, needle aspiration; *P*, partial; *TERB*, terbinafine.
was 11.27 ± 9.47 months. Overall, immunosuppression was not reduced during antifungal therapy. One patient (patient 9) had severe disease and the calcineurin inhibitor and the adjuvant drug azathioprine were withdrawn because of lack of response to partial surgical excision and itraconazole therapy.

**Disease course**

Patients were followed for a mean period of 25.4 months (range 5-84). At the last outpatient visit 12 patients (70.6%) had completed the prescribed treatment and two patients (11.8%, patients 9 and 12) were still receiving antifungal therapy with complete disease remission. The mean follow-up time after finishing the prescribed treatment was 21.2 months (range 2-60). At the end of the study, 11 of the 12 patients had been followed up for at least 6 months posttherapy completion. None of these patients had relapsing disease at a mean follow-up time of 17.5 months (range 1-54), but one patient (5.9%, patient 10) had a de novo disease 12 months after completion of the treatment course for a previous episode of phaeohyphomycosis. There was a single patient who completed the prescribed treatment but had been followed up for less than 6 months (patient 16). He presented with complete disease remission 2 months after finishing the prescribed treatment. During the follow-up period, 3 patients (17.6%) discontinued participation in the study. One patient (5.9%, patient 3) lost his graft because of chronic allograft nephropathy 2 years after starting antifungal treatment with partial remission of the disease. Another patient (5.9%, patient 5) died as a result of bacterial septicemia with a functioning graft 21 months after discontinuation of antifungal therapy with no evidence of active disease. The final patient (5.9%, patient 6) moved out of the city. Treatment failure was not observed in the cohort of patients presented in this study.

**Graft function**

As a measure of graft function after phaeohyphomycosis treatment, serum creatinine levels were...
monitored (Fig 3). Renal allograft function was stable in 13 patients (76.5%). In comparison with pretreatment baselines, serum creatinine levels did not increase after phaeohyphomycosis treatment in 11 patients (64.7%) whereas two patients (11.8%) showed an elevation; however, the increase was not significant. A significant reduction in renal function was observed in 4 patients (23.5%); a histologically proven chronic allograft nephropathy was responsible for decreased function in one patient (5.9%) whereas one (5.9%) occurred after a short course of conventional amphotericin B and two (11.8%) were caused by unknown reasons.

**DISCUSSION**

Dematiaceous fungal infection may cause clinically heterogeneous diseases. Chromoblastomycosis, mycetoma, and phaeohyphomycosis are possible presentations and are mostly defined based on histologic findings. Chromoblastomycosis is caused by a small group of dematiaceous fungi that produce characteristic sclerotic bodies in superficial tissues resulting in verrucous masses. Mycetoma is a deep-tissue infection characterized by tumorous growth of the skin with draining sinuses and histologically by the presence of hyphae grains. In contrast to the former diseases, in phaeohyphomycosis the fungi present as hyphal elements or yeastlike cells with less uniform clinical presentations. Most subcutaneous lesions of phaeohyphomycosis exhibit dense collagen deposition around a collection of polymorphic nuclear leukocytes and necrotic cells surrounded by palisading macrophages and inflammatory cells (pseudocysts). This condition encompasses a group of disorders with superficial, cutaneous, subcutaneous, or systemic involvement.

The great majority of dematiaceous fungi implicated in human disease are considered opportunistic pathogens. The melanin pigment common to all dematiaceous fungi has been implicated as virulence factor with pathogenic potential, even in immunocompetent hosts. Melanin acts as a scavenger of free radicals and hypochlorite, and inhibits hydrolytic enzymes produced by phagocytic cells. Dematiaceous fungi are ubiquitous and most of the species are distributed worldwide. Exposure is thought to be from inhalation or minor trauma and most, if not all, individuals are exposed to them.

With the growing number of patients who are immunocompromised, more dematiaceous fungi species are being reported as the cause of human disease. Revankar et al analyzed 72 cases of disseminated phaeohyphomycosis and found solid organ transplantation as an important risk factor. Indeed, the incidence of fungal infections after solid organ transplantations ranges from 5% among recipients of kidney transplantation to as high as 40% among liver recipients, with high overall mortality rates. In 1974, Ajello et al isolated a black fungus from a single nodule present in the right arm of a patient 19 months after transplantation; this was likely the first description of a subcutaneous phaeohyphomycotic cyst in a kidney transplant recipient. The prevalence of phaeohyphomycosis among kidney transplant recipients has been difficult to establish. The overall number of kidney transplant recipients with dematiaceous fungal infection is small. Moreover, fungal taxonomy is constantly evolving and some experts still disagree on taxonomic issues, such as the true melanin content of *Scedosporium prolificans*, which represents additional challenges. Using mostly pathological findings, Mesa et al found that the prevalence of phaeohyphomycosis in a cohort of 1464 kidney transplant recipients from Colombia was 0.34%. In our prospective study, 3885 kidney transplant recipients were enrolled, finding the prevalence of phaeohyphomycosis was 0.44%.

To date, there are 36 published cases of subcutaneous phaeohyphomycosis in kidney transplant recipients. *Exophiala*, *Alternaria*, and *Phialophora* were the more common causative agents. In our series, *Exophiala* was identified in two patients (11.8%), *Alternaria* in one (5.9%), and *Phialophora* in one (5.9%). Although there are species that do appear to be geographically restricted, such as *Ramichloridium mackenziei*, in the Middle East, all the species found in our study are reported to have a worldwide distribution. For the Brazilian population, limited information about the
mycology of dematiaceous fungi infection in kidney transplant recipients is available. In 1979, Porto et al.\(^1\) described the first case of phaeohyphomycosis caused by *Phialophora bubakii* in a kidney transplant recipient from Brazil. Subsequent to this pioneering report, *Exophiala dermatitidis* was identified in one patient in 1986,\(^1\) *Exophiala jeanselmei* in 3 patients in 1994,\(^2\) *Colletotrichum crassipes* in one patient in 2001,\(^3\) and *Veronaea botryosa* in one patient in 2004.\(^4\) Therefore, the small number of kidney transplant recipients with phaeohyphomycosis precludes speculation about a possible correlation of the distribution of phaeohyphomycosis causative agents within specific Brazilian geographic areas.

Infectious diseases associated with dematiaceous fungi are pleomorphic in solid organ recipients. Physiopathology usually follows a typical pattern of disease progression with lesions beginning as a solid granuloma and later evolving to a cavitary abscess, also known as a phaeohyphomycotic cyst. The most common sites of involvement are the subcutaneous tissues of distal limbs, such as the feet and arms.\(^4\) Environmental exposure to the fungus through a breakdown of normal barriers (eg, inoculation after trauma or during surgery) is proposed to be a significant risk factor for dematiaceous fungi infection. The higher proportion of male patients (70.6%) observed in our series also suggests an occupational risk for this disease, although surprisingly none of our 17 patients reported a previous episode of minor trauma with skin injury.

Clinical presentation with more than one subcutaneous cyst was observed in only 5 of our patients (29.4%) and none of them presented with disseminated phaeohyphomycosis. It is well known that immunophilin-targeting immnosuppressive drugs were originally developed apart from their original antifungal properties.\(^5\) These drugs influence the predominant clinical manifestation of fungal infections; however, they do not affect the incidence of opportunistic infection.\(^6\) In a recent investigation, calcineurin inhibitor agents were independently associated with lower mortality among solid organ recipients with *Cryptococcus neoformans* infection.\(^7\) Unfortunately, no information is available regarding the susceptibility of dematiaceous fungi to the antifungal activity of calcineurin inhibitor drugs. It is interesting to note that among 72 cases of disseminated phaeohyphomycosis compiled by Revankar et al.\(^8\) in 2002, only 6 had received a solid organ transplant. In addition, there is only a single published case report of disseminated phaeohyphomycosis in a kidney transplant recipient receiving calcineurin inhibitor therapy.\(^9\) Calcineurin inhibitors were a part of the immunosuppressive protocol administered to all patients enrolled in this study and the causative agents isolated from our patients have been previously implicated in disseminated phaeohyphomycosis.\(^3\) These observations indicate that disseminated phaeohyphomycosis is not a common condition among kidney transplant recipients, and suggest that calcineurin inhibitor drugs may exert a protective effect against the life-threatening invasive disease.

As is the case for many infectious syndromes caused by dematiaceous fungal infection, therapy for subcutaneous phaeohyphomycosis is not standardized. There are no trials comparing different strategies for the treatment of infections caused by dematiaceous fungi. Surgical excision alone of subcutaneous cysts has been successful in a number of cases, but oral systemic therapy with an azole antifungal agent is frequently used in conjunction with surgery.\(^1\) Itraconazole has been the preferred choice for antifungal systemic therapy as the in vitro susceptibilities to this drug of most strains of dematiaceous fungi is high.\(^5\) At our institution all patients received surgical treatment for phaeohyphomycosis and 11 (64.7%) of 17 patients also received systemic antifungal therapy with itraconazole. Although amphotericin B,\(^10\) fluconazole,\(^11\) ketoconazole,\(^12,13\) and 5-fluorocytosine\(^14\), have been proposed for the treatment of phaeohyphomycosis, these drugs were considered as alternative therapy for those patients with severe disease, poor response, or hepatic toxicity to itraconazole.

This study demonstrated that surgical excision of the lesions in combination with itraconazole-based antifungal therapy for at least 6 months was an effective treatment of phaeohyphomycosis in kidney transplant recipients, resulting in a low impact on renal allograft function.

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**REFERENCES**


