Phaeohyphomycosis Caused by Exophiala Species
in Immunocompromised Hosts

Jyh-Ming Liou, Jann-Tay Wang, Min-Hshi Wang, Shei-Shen Wang, and Po-Ren Hsueh

Abstract: Exophiala species are rarely implicated in clinical diseases. In the past 2 years, we have treated phaeohyphomycosis caused by Exophiala species in three immunocompromised patients. Two of these patients presented with subcutaneous abscess or cutaneous verrucous lesions due to Exophiala jeanselmei. The former, an 81-year-old woman, had pulmonary tuberculosis and the latter, a 62-year-old man, had undergone heart transplantation and was receiving immunosuppressive treatment. The third patient, a 62-year-old woman, had acute lymphoblastic leukemia and developed lymphadenitis due to Wangiella (Exophiala) dermatitidis. In each case, the fungus was discovered on a Gram stain of the aspirated material and was identified by conventional tests. One patient died of bacterial pneumonia with acute respiratory distress syndrome and the other two were treated successfully with surgical excision and antifungal agents. With the more frequent and widespread use of immunosuppressive agents, the incidence of Exophiala infection will certainly increase. Surgical excision or debridement with or without antifungal agents may offer the possibility of cure for phaeohyphomycosis due to Exophiala species.

Case Reports

Case 1
An 81-year-old woman developed a prolonged cough and low-grade fever in August 1999. Pulmonary tuberculosis was
diagnosed from characteristic chest roentgenogram findings and a sputum culture positive for *Mycobacterium tuberculosis*. A soft nodule over the medial aspect of the left foot developed 5 months after the start of anti-tuberculosis chemotherapy. The nodule enlarged gradually without obvious symptoms. She was admitted to the hospital because of low-grade fever and jaundice in February 2000. Gram stain of the pus aspirated from the lesion revealed septated hyphae with branches at acute angles. Amphotericin B was administered and her fever gradually improved. At the same time, multiple retroperitoneal lymphadenopathy was found on abdominal sonography and computerized tomography. Lymphoma was suspected, but the patient refused further invasive study. On the 28th hospital day, she died of bacterial pneumonia with acute respiratory distress syndrome.

**Case 2**

A 62-year-old man had undergone an orthotopic heart transplant in 1997 due to ischemic cardiomyopathy. Afterwards, he received immunosuppressant therapy with cyclosporin, prednisolone, and azathioprine. A 4 x 6-cm plaque with a rough surface developed on the dorsum of his right hand (Fig. 1) 10 months after the heart transplant. Filamentous hyphae (Fig. 2) were found on the gram-stained smear of the pus aspirated from the lesion. Histopathologic examination of the skin biopsy showed budding yeast-like cells. Initially, the patient was treated daily with 200 mg itraconazole and topical liquid nitrogen therapy. Six weeks later, the skin lesion had progressed despite medical treatment. Magnetic resonance image of his right hand revealed nodular lesions involving the subcutaneous fat and extensor tendon. He underwent surgery, and a 9 x 6-cm multinodular mass with pus was excised. He received itraconazole for another 6 weeks after the operation, and the skin lesions resolved. During 3 years of follow-up, there was no recurrence of phaeohyphomycosis.

**Case 3**

A 62-year-old woman had two palpable lymph nodes (2 x 2 cm and 1.5 x 1 cm) in the left axilla when acute lymphoblastic leukemia was diagnosed. Histopathologic examination of the excised lymph node revealed budding yeast-like cells, soli-

### Table. Clinical characteristics of three patients with Exophiala infection

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Organism</th>
<th>Site</th>
<th>Underlying condition</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Period of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>81</td>
<td>F</td>
<td>E. jeanselmei</td>
<td>Foot</td>
<td>Pulmonary tuberculosis</td>
<td>Amphotericin B</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>62</td>
<td>M</td>
<td>E. jeanselmei</td>
<td>Hand</td>
<td>Heart transplantation recipient</td>
<td>Itraconazole, debridement, excision</td>
<td>Survived (3 yr)</td>
<td>No recurrence</td>
</tr>
<tr>
<td>3</td>
<td>62</td>
<td>F</td>
<td>W. dermatitidis</td>
<td>Axillary lymph node</td>
<td>ALL (before C/T)</td>
<td>Itraconazole</td>
<td>Survived (2 yr)</td>
<td>No recurrence</td>
</tr>
</tbody>
</table>

**Table Notes:**

- **ALL =** acute lymphoblastic leukemia
- **C/T =** chemotherapy

### Table Notes:

- ALL = acute lymphoblastic leukemia
- C/T = chemotherapy
tary or in chains, within the granulomatous tissue. She took
itraconazole for 4 months, and amphotericin B was adminis-
tered during the neutropenic stage after chemotherapy.
The disease did not recur during the 2-year follow-up
period.

Microbiology
Cultures of the aspirated pus from Cases 1 and 2 on Sabouraud
dextrose agar (BBL Microbiology Systems, Cockeysville, MD,
USA) yielded a black mold after 14 days of incubation at
27°C. The slide culture revealed annelloconidia aggregating
at the apex of the annellides and conidiophores. Biochemical
tests showed hydrolysis of tyrosine but were negative for
casein, hypoxanthine, and xanthine. The organisms grew
slowly (more than 3 weeks) at 37°C but were unable to grow
at 42°C. Based on the mycologic findings, E. jeanesmei was
identified. The culture on Sabouraud dextrose agar of a
specimen from an excised lymph node from Case 3 grew a
black, moist, shiny, and yeast-like colony after 20 days of
incubation at 27°C. Microscopically, sparse conidia had
accumulated at the apex of the phialide and down the sides
of the conidiophore. The isolate had a positive hydrolysis
reaction for tyrosine but was negative for casein, hypoxanthine,
and xanthine. It grew well at both 37°C and 42°C. Based on
the mycologic findings, W. dermatitidis was identified.
Using the E test (AB Biodisk, Solna, Sweden), performed
as previously described [11], identical minimum inhibitory
concentrations (MICs) of the three isolates were determined:
0.032 mg/mL for amphotericin B, 0.25 mg/mL for itraconazole,
and 16 mg/mL for fluconazole.

Discussion
Infection due to Exophiala species is rarely reported in
Taiwan [11]. In our university hospital with 2,000 beds
in northern Taiwan, the first isolate of Exophiala species
was found in 1994 [11]. Since then, a total of 19 isolates
of Exophiala species have been recovered from clinical
samples from 19 patients (including the three patients
in this report). Among these isolates, 16 were collected
during a pseudo-outbreak between 1994 and 1998
[11]. The three cases in the present study all acquired
the infection in the last 3 years, indicating the emerg-
ing nature of this disease entity in Taiwan.

The reported risk factors for Exophiala species infec-
tion include systemic or topical steroid therapy [7, 9],
malignancy [14], diabetes mellitus [6], and prolonged
administration of broad-spectrum antibiotics [15]. The
three patients in this report were all immunocom-
promised. The first patient had recurrent pulmonary
 tuberculosis and possible retroperitoneal malignancy.
The second patient had received immunosuppressants
after heart transplantation. The third patient had newly
diagnosed acute lymphoblastic leukemia. None of the
three patients were HIV positive. This is similar to
findings in other reports [12]. Since T-cells are af-
fected predominantly in patients infected with HIV,
the predominant mycoses in AIDS are those normally
controlled by T-lymphocytes. Granulocytes are involved
primarily in the control of phaeohyphomycosis. This
explains why there are so few cases of phaeohypho-
mycosis in patients who are HIV positive.

Traumatic inoculation has been reported in about
half of patients with subcutaneous phaeohyphomycosis
[9]. However, the patients in our report could not recall
any recent trauma in the affected area. Exophiala species
are the most common etiologic agents in subcu-
taneous phaeohyphomycosis [12]. Clinical infections
due to Exophiala species include mycetoma, subcutane-
ous phaeohyphomycosis, endocarditis, pneumonia, lung
abscess, synovitis, arthritis, peritonitis, esophagitis,
and keratitis [12, 13, 16]. The clinical presentations of
skin infection caused by Exophiala species include cysts
in 57%, plaque type in 22%, nodular lesions in 13%,
impetigo in 4%, and crust in 4% of cases [9]. The first
two of our patients presented with a nodular lesion and
plaque type, respectively. The third patient presented
with lymphadenopathy.

Exophiala dermatitidis has been transferred to the
genus Wangiella [17]. The morphologic distinction
between E. jeanesmei and W. dermatitidis is very difficult
to make. Physiologic and biochemical tests can facili-
tate the process of identification [18]. Both culture
and biochemical tests were used for fungus identifica-
tion in our patients.

Amphotericin B, 5-fluorocytosine, and azoles such as
itraconazole, ketoconazole, and clotrimazole have
been reported to be effective in the treatment of
phaeohyphomycosis [19], but surgical excision or sur-
gercy combined with medical treatment is usually re-
quired [20]. Sudduth et al reviewed 11 cases of
phaeohyphomycosis caused by Exophiala species [16].
Four were treated successfully with surgical excision
alone. Another four were treated successfully with a
combination of surgical excision and antifungal agents.
One patient was treated with amphotericin B, but she
died before E. jeanesmei was identified. Another two
patients were treated successfully with a combination
of surgical excision and itraconazole.

In conclusion, with the more frequent and wide-
spread use of immunosuppressive agents, the inci-
dence of Exophiala infection will certainly increase.
When an immunosuppressed patient presents with
subcutaneous or cutaneous nodules, phaeohypho-
mycosis due to Exophiala species should be
suspected and included in the differential diagnosis.
Surgical excision or debridement with or without
antifungal agents may offer the possibility of a cure for
phaeohyphomycosis due to Exophiala species.
ACKNOWLEDGMENT: We would like to thank Dr. Fa-Chieh Lee for the isolation of *E. jeanselmei* in Case 1.

References