Case-Control Study of Risk Factors for *Penicillium marneffei* Infection in Human Immunodeficiency Virus–Infected Patients in Northern Thailand

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A case-control study was done in Chiang Mai, Thailand, comparing risk-related behavior and exposures in 80 incident cases of disseminated *Penicillium marneffei* infection in patients with AIDS and 160 control patients with AIDS who did not have *P. marneffei* infection. All subjects were admitted to Chiang Mai University Hospital between December 1993 and October 1995. Cases were younger than controls (16–30 years vs. >30 years of age; odds ratio [OR] = 2.22; 95% CI, 1.22–4.07). Patients with a recent history of occupational or other exposure to soil, especially during the rainy season (May to October), were more likely to present with *P. marneffei* infection (OR = 1.91; 95% CI, 1.04–3.52). History of exposure to or consumption of bamboo rats, the only known nonhuman hosts of *P. marneffei*, was not a risk factor for infection. Our data suggest that recent exposure to a potential environmental reservoir of organisms in the soil may be associated with disseminated *P. marneffei* infections among patients with AIDS in Northern Thailand.

*Penicillium marneffei* is the only dimorphic pathogenic organism among >200 species of *Penicillium*. *P. marneffei* can cause systemic mycosis in humans, particularly those who are immunocompromised [1–2]. The first report of *P. marneffei* infection in Thailand included five patients seen at a hospital in Bangkok between 1974 and 1982 [1]. An epidemic of HIV infection has spread dramatically in Thailand since 1989 and has been most severe in Northern Thailand [3].

*P. marneffei* infection has been recognized recently as a very common emerging fungal pathogen in HIV-positive patients living or traveling in Southeast Asia [2, 4]. Between 1988 and 1992, 86 HIV-infected adults had disseminated *P. marneffei* infection diagnosed at Chiang Mai University Hospital in Northern Thailand [2]. *P. marneffei* infection appears to be less common among AIDS patients from nonnorthern areas of Thailand and from other areas in Southeast Asia [5]. *P. marneffei* infection has been recognized as an AIDS-defining opportunistic infection because of its frequency among immunocompromised HIV-infected persons in Southeast Asia [6].

The reservoirs of *P. marneffei* in nature and the exposures leading to human infections with this organism are largely unknown. *P. marneffei* was originally isolated from a bamboo rat, *Rhizomys sinensis*, in Vietnam [7] and subsequently from another species of bamboo rat, *Rhizomys pruinulosus*, in Southern China [8]. The organism was isolated from the lesser bamboo rat, *Cannomys badius*, in Thailand by Ajello et al. [9].

We recently conducted an environmental survey for *P. marneffei* in Northern Thailand. We isolated *P. marneffei* from the lungs, livers, and spleens of two species of bamboo rats in Chiang Mai, *Rhizomys sumatrensis* and *C. badius* [9]. In addition, one soil sample from the burrow of a *R. sumatrensis* bamboo rat was positive for *P. marneffei* [10]. It is not clear whether bamboo rats are important natural reservoirs for transmission of the infection to humans in areas of endemcity or whether the organism resides in soil and bamboo rats are only another natural host infected coincidentally with *P. marneffei*.

The types of exposure leading to infection in humans and the route of entry of *P. marneffei* are also still unclear.

Since relatively little is known about the epidemiological characteristics of and risk factors for *P. marneffei* infection in humans, we performed a case-control study to evaluate the association between environmental exposures and the risk of acquiring *P. marneffei* infection among patients with AIDS in Northern Thailand.

Materials and Methods

The cases were HIV-infected patients with disseminated *P. marneffei* infection who were seen at Chiang Mai University Hospital between December 1993 and October 1995. Diagnosis of HIV infection was made if the patient’s serum was repeatedly reactive by both ELISA (Enzymun-Test Anti-HIV 1 + 2; Boehringer Mannheim GmbH Diagnostica, Mannheim, Germany) and particle-agglutination test (Serodia-HIV; Fujirebio, Tokyo). *P. marneffei* infection was diagnosed by isolation of
the organism from blood, skin biopsy specimen, or other clinical specimens on Sabouraud dextrose agar. Methods used in this study for fungal isolation and mycologic identification of *P. marneffei* have been described previously [11].

Patients eligible for enrollment in the study were those who met the above criteria and who consented to participate, were >16 years of age, and were able to recall the information needed to respond to the questionnaire at the time of enrollment. Cases who had AIDS-related dementia or HIV-related encephalopathy or brain dysfunction were excluded from the study.

For each case, we enrolled two controls. The controls were HIV-infected patients from Chiang Mai University Hospital whose AIDS was diagnosed on the basis of a modified version of the 1989 Centers for Disease Control and Prevention (CDC) definition [12] and who did not have *P. marneffei* infection. For all controls, blood cultures to exclude active *P. marneffei* infection were performed on admission, and none had skin lesions or other clinical findings typical of *P. marneffei* infection. The eligibility and exclusion criteria for the controls were the same as those for the cases.

A standardized questionnaire was used by three trained infection control nurses to interview both cases and controls. Questionnaires sought information about sociodemographic characteristics, AIDS-defining illnesses, occupational status, residential area, history of contact with animals, pet ownership, history of exposure to bamboo thickets and bamboo rats (pictures of two species of bamboo rats, *R. sumatrensis* and *C. badius*, were shown to assist subjects in their identification), and history of smoking cigarettes, marijuana, or opium.

To minimize recall bias and interviewer bias, most of the cases and controls were interviewed during the first few days after admission, while the results of the fungal culture and a definite diagnosis were still pending. The final diagnosis, determined after the fungal culture results became available, was used to determine the case vs. control status of the patients included in the study.

The levels of CD4⁺ lymphocytes were determined by flow cytometry (FACScan, Becton-Dickinson, Towson, MD; and SimulSET software, Becton-Dickinson, San Jose, CA) and on the basis of a complete blood cell count with an automated differential of 10,000 WBCs. A few patients refused to provide a blood specimen or died before the blood could be obtained for lymphocyte subset analysis.

**Data Analysis**

Unmatched univariate odds ratios were calculated with Epi-Info version 6.02 (CDC, Atlanta). A 95% confidence interval was calculated for each odds ratio. Most continuous variables were categorized into two or three subgroups. Variables found to be significant in the univariate analysis and other potential confounding variables were used to fit a multiple logistic regression model.

The multivariate analysis served to control for potential confounders, to evaluate interaction effects, and to determine the independent risk factors associated with *P. marneffei* infection. The standard logistic regression model was used for model fitting [13]. EGRET version 0.19.5 (Statistics and Epidemiology Research Corp., Seattle) was used for performing the multiple logistic regression analysis.

**Results**

A total of 80 HIV-infected patients with microbiologically confirmed *P. marneffei* infection (cases) and 160 AIDS patients without disseminated *P. marneffei* infection (controls) were evaluated. Table 1 presents the AIDS-defining conditions in the cases and controls; some had more than one AIDS-defining illness. Among the controls, 56.9% had cryptococcosis, 24.4% had *Pneumocystis carinii* pneumonia, 15.6% had tuberculosis, 7.5% had toxoplasmosis, and 6.3% had salmonella septicemia.

Other AIDS-defining infections were present in <5% of controls. Among the cases, in addition to *P. marneffei* infection, 5% had cryptococcosis, 2.5% had toxoplasmosis, and 2.5% had *P. carinii* pneumonia.

In our study, cases were younger than controls (16–30 years vs. >30 years of age; OR = 2.22; 95% CI, 1.22–4.07) (table 2). The level of CD4⁺ lymphocytes was not significantly different between cases and controls. There were no significant differences between cases and controls in terms of sex, years of education, rural vs. urban residence, and province of residence (table 2).

The univariate analysis of possible risk factors associated with *P. marneffei* infection included consideration of present

**Table 1.** AIDS-defining illnesses in cases and controls who were patients at Chiang Mai University Hospital, Chiang Mai, Thailand (1995).

<table>
<thead>
<tr>
<th>AIDS indicator</th>
<th>Cases (n = 80)</th>
<th>Controls (n = 160)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidiasis*</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>4 (5)</td>
<td>91 (56.9)</td>
</tr>
<tr>
<td>Cytomegalovirus infection</td>
<td>0</td>
<td>5 (3.1)</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Isosporiasis</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>0</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>0</td>
<td>25 (15.6)</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>1 (1.3)</td>
<td>4 (2.5)</td>
</tr>
<tr>
<td><em>Pneumocystis carinii</em> pneumonia</td>
<td>2 (2.5)</td>
<td>39 (24.4)</td>
</tr>
<tr>
<td><em>P. marneffei</em> infection</td>
<td>80 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Salmonella septicemia, recurrent</td>
<td>0</td>
<td>10 (6.3)</td>
</tr>
<tr>
<td>Toxoplasmosis, recurrent</td>
<td>2 (2.5)</td>
<td>12 (7.5)</td>
</tr>
<tr>
<td>Wasting syndrome</td>
<td>0</td>
<td>7 (4.4)</td>
</tr>
</tbody>
</table>

* Some cases and controls had more than one AIDS-associated disease.

* Of esophagus, trachea, bronchi, or lung.
occupational contact with animals or plants; reported present or past occupational contact with animals or plants; occupational history; exposure to pigs, poultry, or cattle; exposure to domestic animals (cats, dogs, or birds); and smoking of cigarettes, marijuana, or opium (table 3). Current occupational exposure to plants or animals was significantly more common in subjects if they had environmental exposure to and infection with bamboo rats. These rats had been cooked before being eaten.

Cases were more likely to work as farmers or laborers than were controls, but these differences were not statistically significant. Exposure to pigs, poultry, or cattle was not associated with *P. marneffei* infection. In addition, neither exposure to domestic animals (birds, dogs, or cats) nor a history of smoking cigarettes, marijuana, or opium was associated with *P. marneffei* infection in this study (table 3).

We evaluated the differences between cases and controls with respect to their history of exposure to the different species of bamboo rats, their history of eating bamboo rats, how recently they had seen bamboo rats, and whether they had bamboo thickets or forests near their houses or workplaces or a history of digging for raw bamboo shoots (table 4). All of these potential risk factors for exposure to *P. marneffei* were similar among cases and controls. More than 50% of cases and controls had seen bamboo rats near their homes; *C. badius* was more commonly seen than *R. sumatrensis*. A history of eating bamboo rats and the frequency of recently seeing a bamboo rat were not different between the cases and controls. All bamboo rats had been cooked before being eaten.

All of the variables that were significant in the univariate analysis were used to develop a multiple logistic regression model. After adjustment for the statistical contribution of each variable, the final model showed the following factors to be independently associated with an increased risk of *P. marneffei* infection: age of 16–30 years (OR = 2.22; 95% CI, 1.22–4.07) and present occupation involving exposure to plants or animals (OR = 1.91; 95% CI, 1.04–3.52) (table 5).

### Discussion

This is the first case-control study of risk factors for disseminated *P. marneffei* infection, an emerging AIDS-defining infection in Northern Thailand. The disease is very uncommon outside Southeast Asia but is very common among patients with AIDS in Northern Thailand. The case-control method is often the research strategy of choice for investigating the etiology of a rare disease [14, 15]. This study design was used in order to obtain preliminary data so that a causal hypothesis could be developed for subsequent evaluation in other controlled studies.

Chiang Mai, with a population of 1.5 million in 1994, is the largest province in Northern Thailand and has the highest reported incidence of disseminated *P. marneffei* infection in Thailand. All of the cases in this study were patients with newly diagnosed *P. marneffei* infections (i.e., incident cases). The controls were patients with AIDS who were seen in the same hospital during the same study period and had low CD4 lymphocyte counts, similar to those of the cases. This matching was done to ensure that the HIV-infected controls had the same chance as the cases to develop symptomatic *P. marneffei* infection if they had environmental exposure to and infection with *P. marneffei*.

Our study found that cases were younger than controls. This may have occurred because the cases who were younger had engaged in occupations, avocations, and recreation that involved a greater chance of recent exposure to an environmental reservoir of the organism. *P. marneffei* infections are not an early manifestation of AIDS, since the CD4 lymphocyte counts of both cases and controls were very low (most were <50/μL). Cases were also more likely to be male than female, but this difference was not statistically significant. Other demographic factors were not significantly associated with *P. marneffei* infection.

The types of exposure leading to *P. marneffei* infection in humans and the route of entry of the organism are unknown. By analogy with other opportunistic fungal pathogens, it seems quite likely that *P. marneffei* conidia may be inhaled from a contaminated reservoir in the environment and subsequently disseminate from the lungs when immunosuppression occurs in the infected host [1, 4].

### Table 2. Distribution of sociodemographic characteristics and CD4 lymphocyte levels in AIDS patients with *P. marneffei* infection (cases) and control AIDS patients in Chiang Mai, Thailand (1995).

<table>
<thead>
<tr>
<th>Characteristic (%)</th>
<th>Cases (n = 80)</th>
<th>Controls (n = 160)</th>
<th>Crude OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16–30 y</td>
<td>53 (66.3)</td>
<td>75 (46.9)</td>
<td>2.22 (1.22–4.07)</td>
</tr>
<tr>
<td>≥31 y</td>
<td>27 (33.8)</td>
<td>85 (53.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>71 (88.8)</td>
<td>128 (80.0)</td>
<td>1.97 (0.84–4.77)</td>
</tr>
<tr>
<td>Female</td>
<td>9 (11.3)</td>
<td>32 (20.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>No. of CD4+ lymphocytes/μL*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–50</td>
<td>52 (71.2)</td>
<td>81 (63.3)</td>
<td>1.50 (0.50–4.70)</td>
</tr>
<tr>
<td>51–100</td>
<td>15 (20.5)</td>
<td>33 (25.8)</td>
<td>1.06 (0.47–2.30)</td>
</tr>
<tr>
<td>≥100</td>
<td>6 (8.2)</td>
<td>14 (10.9)</td>
<td>1.0</td>
</tr>
<tr>
<td>Present residence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>45 (56.3)</td>
<td>98 (61.3)</td>
<td>0.81 (0.46–1.45)</td>
</tr>
<tr>
<td>Urban</td>
<td>35 (43.8)</td>
<td>62 (38.8)</td>
<td>1.0</td>
</tr>
<tr>
<td>Years of education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤6</td>
<td>48 (60.0)</td>
<td>101 (63.1)</td>
<td>0.88 (0.48–1.59)</td>
</tr>
<tr>
<td>≥7</td>
<td>32 (40.0)</td>
<td>59 (36.9)</td>
<td>1.0</td>
</tr>
<tr>
<td>Present province of residence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chiang Mai</td>
<td>73 (91.3)</td>
<td>132 (82.5)</td>
<td>2.21 (0.87–5.87)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (8.7)</td>
<td>28 (17.5)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* CD4+ lymphocytes were not measured in 32 controls and seven cases.
Table 3. Univariate analysis of risk factors in cases and controls, hospitalized at Chiang Mai University Hospital, Chiang Mai, Thailand (1995).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Cases (n = 80)</th>
<th>Controls (n = 160)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present occupational exposure to animal and/or plant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33 (41.3)</td>
<td>43 (26.9)</td>
<td>1.91 (1.04–3.52)</td>
</tr>
<tr>
<td>No</td>
<td>47 (58.8)</td>
<td>117 (73.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Present or past occupational exposure to animal and/or plant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>33 (41.3)</td>
<td>43 (26.9)</td>
<td>1.69 (0.88–3.23)</td>
</tr>
<tr>
<td>Past</td>
<td>12 (15.0)</td>
<td>40 (25.0)</td>
<td>0.66 (0.29–1.50)</td>
</tr>
<tr>
<td>Never</td>
<td>35 (43.7)</td>
<td>77 (48.1)</td>
<td>1.0</td>
</tr>
<tr>
<td>Present occupation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Farmer</td>
<td>17 (21.3)</td>
<td>25 (15.6)</td>
<td>1.71 (0.76–3.88)</td>
</tr>
<tr>
<td>Laborer</td>
<td>34 (42.5)</td>
<td>62 (38.8)</td>
<td>1.38 (0.73–2.63)</td>
</tr>
<tr>
<td>Other</td>
<td>29 (36.2)</td>
<td>73 (45.6)</td>
<td>1.0</td>
</tr>
<tr>
<td>Ever having a:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pig farm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (10.0)</td>
<td>17 (10.6)</td>
<td>0.93 (0.35–2.43)</td>
</tr>
<tr>
<td>No</td>
<td>72 (90.0)</td>
<td>143 (89.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Poultry farm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22 (27.5)</td>
<td>34 (21.3)</td>
<td>1.41 (0.72–2.73)</td>
</tr>
<tr>
<td>No</td>
<td>58 (72.5)</td>
<td>126 (78.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Cattle farm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (10.0)</td>
<td>24 (15.0)</td>
<td>0.63 (0.25–1.57)</td>
</tr>
<tr>
<td>No</td>
<td>72 (90.0)</td>
<td>136 (85.0)</td>
<td>1.0</td>
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<tr>
<td>Dog(s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>58 (72.5)</td>
<td>106 (66.3)</td>
<td>1.34 (0.72–2.53)</td>
</tr>
<tr>
<td>No</td>
<td>22 (27.5)</td>
<td>54 (33.8)</td>
<td>1.0</td>
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<tr>
<td>Cat(s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25 (31.2)</td>
<td>45 (28.1)</td>
<td>1.16 (0.62–2.17)</td>
</tr>
<tr>
<td>No</td>
<td>55 (68.8)</td>
<td>115 (71.9)</td>
<td>1.0</td>
</tr>
<tr>
<td>Bird(s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12 (15.0)</td>
<td>33 (20.6)</td>
<td>0.68 (0.31–1.47)</td>
</tr>
<tr>
<td>No</td>
<td>68 (85.0)</td>
<td>127 (79.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Ever smoking:</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Cigarettes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>53 (66.2)</td>
<td>116 (72.5)</td>
<td>0.74 (0.40–1.38)</td>
</tr>
<tr>
<td>No</td>
<td>27 (33.8)</td>
<td>44 (27.5)</td>
<td>1.0</td>
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<tr>
<td>Marijuana</td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25 (31.2)</td>
<td>38 (23.7)</td>
<td>1.46 (0.77–2.76)</td>
</tr>
<tr>
<td>No</td>
<td>55 (68.8)</td>
<td>122 (76.3)</td>
<td>1.0</td>
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<tr>
<td>Opium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (10.0)</td>
<td>11 (6.9)</td>
<td>1.51 (0.53–4.26)</td>
</tr>
<tr>
<td>No</td>
<td>72 (90.0)</td>
<td>149 (93.1)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

The incubation periods of disseminated *P. marneffei* infection described in a few studies have been quite variable. Persons with apparently long periods of asymptomatic infection with *P. marneffei* prior to reactivation have been reported [16]. Other cases have been reported in which the clinical appearance of disseminated infections occurred within a few weeks of exposure to the organism [17]. The appearance of *P. marneffei* infection in infants and young children with AIDS suggests that the duration between infection and dissemination of *P. marneffei* sometimes may be brief [18]. Each clinical case of *P. marneffei* infection might represent the outcome of three possible processes: primary infection, reinfection, or reactivation of latent disease. Primary infection appears to be an important problem among children with perinatal HIV infection [17]. In adults with disseminated *P. marneffei* infections who live in an area of endemicity, the infection could result from reactivation of latent infections, reinfection, or primary infection.

Our data, which show an increased risk associated with recent soil contact, suggest that many AIDS patients with dissem-
Table 4. Exposure of cases and controls to potential risk factors for *P. marneffei* infection (Chiang Mai, Thailand, 1995).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>No. (%) of:</th>
<th>Crude OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n = 80)</td>
<td>Controls (n = 160)</td>
</tr>
<tr>
<td>Species of bamboo rats seen*</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>R. sumatrensis</em></td>
<td>19 (23.8)</td>
<td>28 (17.5)</td>
</tr>
<tr>
<td><em>C. badius</em></td>
<td>49 (61.3)</td>
<td>82 (51.3)</td>
</tr>
<tr>
<td>None</td>
<td>27 (33.8)</td>
<td>63 (39.4)</td>
</tr>
<tr>
<td>Ever eaten bamboo rat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>25 (31.3)</td>
<td>45 (28.1)</td>
</tr>
<tr>
<td>No</td>
<td>55 (68.7)</td>
<td>115 (71.9)</td>
</tr>
<tr>
<td>Last time bamboo rat seen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>£1 y ago</td>
<td>17 (37.0)</td>
<td>29 (29.8)</td>
</tr>
<tr>
<td>2–5 y ago</td>
<td>16 (34.8)</td>
<td>30 (31.9)</td>
</tr>
<tr>
<td>≥6 y ago</td>
<td>13 (28.2)</td>
<td>36 (38.3)</td>
</tr>
<tr>
<td>Bamboo thickets close to present house</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>39 (48.8)</td>
<td>81 (50.6)</td>
</tr>
<tr>
<td>No</td>
<td>41 (51.3)</td>
<td>79 (49.4)</td>
</tr>
<tr>
<td>Bamboo thickets close to present workplace</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>18 (22.5)</td>
<td>34 (21.3)</td>
</tr>
<tr>
<td>No</td>
<td>62 (77.5)</td>
<td>126 (78.8)</td>
</tr>
<tr>
<td>Digging for bamboo shoots</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>16 (20.0)</td>
<td>26 (16.3)</td>
</tr>
<tr>
<td>Ever</td>
<td>37 (46.3)</td>
<td>73 (45.6)</td>
</tr>
<tr>
<td>Never</td>
<td>27 (33.8)</td>
<td>61 (38.1)</td>
</tr>
<tr>
<td>Forest close to present house</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23 (28.8)</td>
<td>52 (32.5)</td>
</tr>
<tr>
<td>No</td>
<td>57 (71.3)</td>
<td>108 (67.5)</td>
</tr>
<tr>
<td>Forest close to present workplace</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22 (27.5)</td>
<td>34 (21.3)</td>
</tr>
<tr>
<td>No</td>
<td>58 (72.5)</td>
<td>126 (78.8)</td>
</tr>
</tbody>
</table>

* Some cases and controls saw both types of bamboo rat.

Table 5. Unconditional logistic regression analysis of selected risk factors for *P. marneffei* infection in HIV-infected patients at Chiang Mai University Hospital, Chiang Mai, Thailand (1993–1995).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (16–30 y vs. ≥31 y)</td>
<td>2.18 (1.24–3.82)</td>
</tr>
<tr>
<td>Occupational exposure to plants or animals vs. none</td>
<td>1.85 (1.04–3.30)</td>
</tr>
</tbody>
</table>

inated *P. marneffei* infection may have acquired the infection recently, after the onset of immunosuppression.

To evaluate risk factors for *P. marneffei* infection, we investigated a number of possible exposures, including occupation, occupational contact with agriculture or farm animals, type of animal contact, domestic pet ownership, and history of smoking cigarettes, marijuana, or opium. Because the incubation period of the disease is unknown, we inquired about both recent and remote exposures. Our data indicate that patients who have had recent occupational exposure to animals or plants have a greater risk of developing symptomatic *P. marneffei* infection when they develop AIDS than do patients without such exposure.

However, when we compared the risk of symptomatic *P. marneffei* infection among patients with AIDS who had ever worked around animals or plants (including those with more remote exposure) to that for patients who had not, there was no longer a significant association. This suggests that current occupational exposure to animals or plants—which may involve exposure to a reservoir of the organism in the soil—among HIV-infected patients who are already immunosuppressed may be critical to whether they develop *P. marneffei* infection as an AIDS-defining illness.

Even though cases were more likely to be farmers or laborers than were controls, the difference was not statistically significant. Having pig, poultry, or cattle farms and owning pets (dogs, cats, or birds) also were not risk factors for infection. Subjects with a history of having smoked marijuana or opium
had a slightly increased risk of penicilliosis, but this risk was not statistically significant.

We have observed a seasonal variation in disseminated *P. marneffei* infections in HIV-infected patients among persons admitted to Chiang Mai University Hospital [19]. *P. marneffei* infections were significantly more frequent during the rainy season (i.e., between May and October) in patients hospitalized between 1991 and 1994; among AIDS patients with *Cryptococcus neoformans* infections, no seasonal variation was observed (OR for *P. marneffei* infection vs. *C. neoformans* infection in the rainy season = 1.90; 95% CI, 1.3–2.8).

Bamboo rats are common in hilly and mountainous areas in Northern Thailand and live underground. They are the only animals other than humans that have been found to be infected with *P. marneffei* in nature. In an environmental survey for the reservoir of *P. marneffei* in Chiang Mai Province, we found the fungus in the internal organs of two species of bamboo rats; 3 of 10 *C. badius* and 13 of 14 *R. sumatrensis* rats were infected, and we isolated *P. marneffei* from one soil sample from an *R. sumatrensis* rat’s burrow [10].

In our case-control study, we found that more than half of the cases and controls had seen bamboo rats and more than 25% had eaten them in the past. *C. badius* rats were seen more often than *R. sumatrensis* rats. However, we could not demonstrate an association between these potential exposures or contacts with bamboo rats and *P. marneffei* infections. These data could indicate that both bamboo rats and humans acquire the organism from common environmental sources in the soil; they do not suggest that bamboo rats are a reservoir for *P. marneffei* infection in humans.

Bamboo is a common plant that grows in rural areas in Northern Thailand and is also a favorite food of the Thai people. The habitat of *R. sumatrensis* is under bamboo thickets, while *C. badius* may live under many kinds of plants in forests or rice fields [9, 10]. However, we could not demonstrate a significant association between exposure to bamboo thickets or forests and *P. marneffei* infection. Bamboo thickets are common in rural areas of Northern Thailand; however, they might be an environmental reservoir of *P. marneffei* in only some areas. Therefore, the absence of a significant association between this type of exposure and *P. marneffei* infection may not be definitive.

The logistic regression model contained only two significant covariates. The adjusted odds ratio for *P. marneffei* infection associated with current occupational exposure to plants or animals, after adjustment for age, remained significant (OR = 1.85; 95% CI, 1.04–3.30). No significant interactions were found for sex or CD4+ lymphocyte count. However, the use of a case-control study to identify risk factors for disseminated mycosis, which may have a very long latency period, and to identify potential risk factors when they are very common in the population at risk may not always succeed in demonstrating the critical risk behaviors for development of systemic mycosis [20].

Four potential sources of bias may have been present in this case-control study. Cases and controls who volunteered to participate in the study may differ from those who refused to join the study, in terms of their exposures. However, nearly all the cases and controls who met our eligibility criteria were enrolled and studied. Differential referral bias may have occurred between cases and controls because many of the hospitals in Chiang Mai and nearby provinces refer the most serious or complicated cases to Chiang Mai University Hospital. However, AIDS in both cases and controls was diagnosed on the basis of the same clinical definition, and both were seen by the same group of physicians. In addition, it is not apparent that referral patterns would be associated with environmental exposures.

Differential misclassification of disease can occur and can bias (increase or decrease) the relative odds estimate. Although all of our cases and controls were examined for *P. marneffei* infections by hemoculture, it is possible that some of the controls were infected with *P. marneffei* but that it was obscured in culture by the more rapid growth of another pathogen. However, since both cases and controls were HIV-infected and had similar impairment of cell-mediated immunity, as estimated by their CD4+ lymphocyte counts, controls who were exposed to *P. marneffei* in the environment should have had a chance equal to that for cases of developing symptomatic *P. marneffei* infection. We did not include AIDS patients with clinical symptoms of *P. marneffei* infection in our control group, even if their culture for the fungus was negative.

Cases could have remembered their exposures better than controls. However, the sources of *P. marneffei* in the environment and the exposures leading to infection are not known at present. Nevertheless, it may be difficult to identify important exposures if primary infection has occurred several years prior to the clinical dissemination of *P. marneffei* infection and HIV infection.

Interviewer bias in our study could have occurred, since ~70% of the patients infected with *P. marneffei* have skin lesions [21]. However, other systemic mycoses may also present with skin lesions. In addition, this exploratory study did not have a well-defined hypothesis regarding the critical reservoir or exposure leading to infection that might have biased the patients or interviewers.

Our data suggest that soil exposure, especially during the rainy season, may be important in patients who have recently acquired primary infection. Exposure to bamboo rats would appear not to be important in the development of disseminated infection in this population.

References


