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# Histoplasmosis and penicilliosis: Comparison of clinical features, laboratory findings and outcome

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Received 24 May 2004; received in revised form 21 September 2004; accepted 11 October 2004

Corresponding Editor: Michael Ellis, Al Ain, UAE

## KEYWORDS

Histoplasmosis;  
Penicilliosis marneffeii;  
Acquired  
immunodeficiency  
syndrome

## Summary

**Introduction:** Histoplasmosis and penicilliosis are infections caused by the dimorphic fungi, *Histoplasma capsulatum* and *Penicillium marneffeii*, respectively. The aim of this study was to compare the clinical presentation, laboratory and radiologic findings and outcome of these infections at Srinagarind Hospital, Khon Kaen, Thailand.

**Methods:** The medical records of patients who had positive cultures for *Histoplasma capsulatum* and *Penicillium marneffeii* during 1996–2002 were reviewed. The data were compared and analyzed by the Chi-square and Fisher's exact tests.

**Results:** There were 32 and 36 medical records of patients with *H. capsulatum* and *P. marneffeii* infection, respectively, available for review. The most common underlying disease of patients with histoplasmosis and penicilliosis was acquired immunodeficiency syndrome (AIDS), which accounted for 90.6% and 91.7%, respectively. The most common clinical findings in both infections were fever, weight loss, cough, anemia, lymphadenopathy, hepatomegaly and splenomegaly. Frequencies of skin lesions were not statistically different between either group ( $P = 0.20$ ). Laboratory findings were similar between the two infections, except hyperbilirubinemia, which was more common in the penicilliosis group ( $P = 0.02$ ). There were similar abnormal X-ray findings in both groups with interstitial infiltration the most common abnormality.

**Conclusions:** Histoplasmosis and penicilliosis had similar clinical presentations, laboratory findings and chest X-ray abnormalities. Itraconazole is recommended as secondary prophylaxis in HIV-infected patients who have histoplasmosis or penicilliosis.

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## Introduction

Histoplasmosis and penicilliosis are infections caused by the dimorphic fungi, *Histoplasma capsulatum* and *Penicillium marneffeii*, respectively. They can cause clinical disease both in normal and immunocompromised hosts, including those with acquired immunodeficiency syndrome (AIDS), systemic lupus erythematosus, corticosteroid or immunosuppressive agent use.<sup>1–4</sup>

In Thailand, penicilliosis is more common than histoplasmosis.<sup>5</sup> According to the Ministry of Public Health of Thailand, the cumulative number of AIDS patients during 1984–2004 with penicilliosis was 6323 and with histoplasmosis was 631. Because both fungi are yeast forms in stained clinical specimens, they are difficult to differentiate. In fungal culture media, *H. capsulatum* grows more slowly than *P. marneffeii*. This may explain the lower incidence of histoplasmosis in Thailand, where experienced personnel and good laboratory facilities are lacking.

The objective of this study is to present the authors' experience of the initial presentations, laboratory findings and outcome in patients with histoplasmosis and penicilliosis. This may be helpful for clinicians who are not familiar with either of these fungi. This is also the first report comparing both infections in the literature.

## Materials and methods

### Setting

The Srinagarind Hospital is a 700-bed university teaching hospital affiliated with Khon Kaen University, providing healthcare for a population of nearly 1,500,000 inhabitants. There are approximately 32,000 admissions and 490,000 visits to the outpatient clinic each year.

### Study design

The medical records of patients with clinical evidence of infection during 1996–2002 and who had a positive culture of *Histoplasma capsulatum* or *Penicillium marneffeii* from a clinical specimen were retrospectively reviewed. Patients who were less than 15 years old were excluded. The epidemiological data, clinical features, laboratory findings and outcome were collected.

### Microbiological methods

Blood samples were processed in the BacT/Alert (Organon Teknika, Durham, NC, USA) continuous-monitoring blood culture system. Cultures of clinical specimens, such as sputum, lymph node tissue, and bone marrow were performed on Sabouraud's dextrose agar at 25 °C. Isolates that were visible within two or three days of incubation were subcultured on brain-heart infusion agar and incubated at 37 °C. Positive cultures for *P. marneffeii* and *H. capsulatum* were characterised as dimorphic fungi that grew as a mold at 25 °C and as a yeast at 37 °C. Methods of identification and mycological characteristics of these fungi are described elsewhere.<sup>2–3</sup>

### Statistical analysis

Data were entered and analyzed with SPSS Professional Statistics, version 11.0. Comparability between the groups was assessed by analysis with Chi-square and Fisher's exact tests for categorical variables and Student's *t* test for continuous variables. *P* values <0.05 were considered to be significant.

## Results

During the seven-year period, there were 34 and 36 patients who had positive cultures for *H. cap-*

**Table 1** Age, sex, and underlying diseases of patients with histoplasmosis and penicilliosis at Srinagarind Hospital, Thailand 1996–2002.

	Number of patients	
	Histoplasmosis ( <i>n</i> = 32)	Penicilliosis ( <i>n</i> = 36)
Age in years (mean ± SD)	32.9 ± 6.8	34.4 ± 9.7
Sex (male:female)	3.6:1	4.1:1
Underlying disease		
Acquired immunodeficiency syndrome	29	33
Connective tissue disease	1	1
Diabetes mellitus	0	1
Nontuberculous mycobacterial disease	1	1
No underlying disease	1	0

**Table 2** Clinical features of patients with histoplasmosis and penicilliosis at Srinagarind Hospital, Thailand 1996–2002.

Clinical features	Number of patients (%)		P value
	Histoplasmosis (n = 32)	Penicilliosis (n = 36)	
Fever	31 (96.8)	34 (94.4)	0.62
Weight loss	27 (84.4)	32 (88.9)	0.58
Diarrhea	9 (28.1)	11 (30.5)	0.82
Abdominal pain	4 (12.5)	16 (44.4)	0.003
Cough	13 (40.6)	18 (50.0)	0.43
Bleeding	1 (3.1)	2 (5.5)	0.62
Hypotension (BP <90/60 mmHg)	12 (37.5)	3 (8.3)	0.01
Anemia	29 (90.6)	34 (94.4)	0.54
Jaundice	4 (12.5)	2 (5.5)	0.31
Lymphadenopathy	24 (75.0)	15 (41.7)	0.005
Hepatomegaly	21 (65.6)	25 (69.4)	0.49
Splenomegaly	12 (37.5)	20 (55.5)	0.13
Skin lesions	12 (37.5)	19 (52.8)	0.20
Plaques/papules	5 (15.6)	1 (2.8)	0.06
Umbilicated papules	4 (12.5)	13 (33.3)	0.02
Ulcers	2 (6.2)	1 (2.8)	0.48
Maculopapular rash	1 (2.8)	0	0.28
Vesicles	0	1 (2.8)	0.34
Pustules	0	1 (2.8)	0.34
Subcutaneous abscess	0	2 (5.6)	0.17

*sulatum* and *P. marneffeii* respectively, and 32 and 36 sets of medical records respectively, available for data review. Age, sex, and underlying diseases are detailed in Table 1. There was no mixed infection of both fungi found in the study period. However, there were four cases with concurrent bacteremia (*Streptococcus* group B 1, *Salmonella* 1, *Serratia* 1, *Enterobacter* 1) and two with cryptococcal meningitis in the histoplasmosis group. There were two cases of *Salmonella* bacteremia and three cases of cryptococcal meningitis in the penicilliosis group.

The most common underlying disease was AIDS, accounting for 90.6% and 91.7% of the underlying disease in each group, respectively.

Clinical features are presented in Table 2. The most common symptoms in both groups of patients were fever, weight loss and cough. Abdominal pain was more common in penicilliosis patients ( $P < 0.05$ ). The common physical findings in both groups were anemia, lymphadenopathy, hepatomegaly and splenomegaly. Hypotension and lymphadenopathy were more common in patients with histoplasmosis than penicilliosis ( $P < 0.05$ ). Skin lesions were found equally in both penicilliosis and histoplasmosis patients ( $P = 0.20$ ). However, umbilicated papules were more common in the penicilliosis group ( $P < 0.05$ ).

Laboratory findings in both infections are shown in Table 3. Hematologic abnormalities were com-

**Table 3** Laboratory findings of patients with histoplasmosis and penicilliosis at Srinagarind Hospital, Thailand 1996–2002.

Laboratory findings	Number of patients (%)		P value
	Histoplasmosis (n = 32)	Penicilliosis (n = 36)	
Anemia (hemoglobin <10 g/dl)	21/30 (70.0)	29/35 (82.8)	0.22
Neutropenia (WBC <3 × 10 <sup>9</sup> /L)	8/30 (20.7)	7/35 (20.0)	0.52
Thrombocytopenia (platelets <100 × 10 <sup>9</sup> /L)	10/30 (33.3)	14/35 (40.0)	0.57
Pancytopenia	2/30 (6.7)	6/35 (17.1)	0.19
Hypercalcemia (Ca >10 g/dl)	0/17 (0.0)	0/2 (0.0)	–
Hypoalbuminemia (albumin <2.5 g/dl)	12/26 (46.1)	21/30 (70.0)	0.47
Hyperbilirubinemia (total bilirubin >2.0 g/dl)	3/27 (11.1)	11/30 (36.7)	0.02
SGPT elevation (>5 times UNL)	1/27 (3.7)	1/30 (3.3)	0.94
Alkaline phosphatase elevation (>3 times UNL)	14/27 (51.8)	18/29 (62.1)	0.44

UNL = upper normal limit.

**Table 4** Results of microscopic diagnosis and cultures of patients with histoplasmosis and penicilliosis at Srinagarind Hospital, Thailand 1996–2002.

	Number of patients (%)	
	Histoplasmosis (n = 32)	Penicilliosis (n = 36)
Positive microscopic exam	32/32 (100.0)	36/36 (100.0)
Bone marrow	23/23 (100.0)	21/21 (100.0)
Sputum	5/12 (41.7)	5/10 (50.0)
Pleural fluid	0/1 (0.0)	0/3 (0.0)
Pus or skin scraping	12/12 (100.0)	18/19 (94.7)
Lymph node	13/13 (100.0)	7/7 (100.0)
Positive cultures	32/32 (100.0)	36/36 (100.0)
Blood	0/30 (0.0)	16/35 (45.7)
Bone marrow	23/23 (100.0)	19/21 (90.4)
Sputum	0/12 (0.0)	1/10 (10.0)
Pleural fluid	0/1 (0.0)	2/3 (67.7)
Pus or skin scraping	2/2 (100.0)	8/9 (88.9)
Lymph node	3/13 (23.1)	7/7 (100.0)

mon. Hyperbilirubinemia was more common in the penicilliosis group than in the histoplasmosis group ( $P < 0.05$ ).

Table 4 shows the results of microscopic examination and cultures of specimens. Bone marrow fluid culture was positive in all histoplasmosis patients and 90.4% of penicilliosis patients. Hemoculture was negative in all histoplasmosis patients but positive in 50% of penicilliosis patients.

Table 5 demonstrates radiographic findings in both groups. There were no differences in abnormalities seen on chest X-rays in either group ( $P = 0.38$ ).

There were 30 cases of histoplasmosis and 34 cases of penicilliosis admitted to the hospital that were given amphotericin B intravenously at a dose of 0.7 mg/kg/day. Three cases with histoplasmosis and five cases with penicilliosis died in the hospital, accounting for in-hospital mortality of 10% and 14.7%, respectively. The other 27 cases of histoplasmosis and 29 cases of penicilliosis were discharged from the hospital and received oral itraconazole

400 mg/day as maintenance therapy initially for three months then 200 mg/day afterwards. The median duration of follow up for patients with histoplasmosis was longer than the follow up of patients with penicilliosis, (9.5 months (range 0.5–40 months) versus 22 months (range 1–75 months)) respectively ( $P < 0.05$ ). No patient had a relapse on itraconazole maintenance therapy.

## Discussion

Histoplasmosis and penicilliosis are serious opportunistic fungal infections in AIDS patients. Histoplasmosis is endemic in certain parts of the world, such as the USA and South America, but there are only a few reports of histoplasmosis in Thailand despite the AIDS epidemic.<sup>6–8</sup> However, penicilliosis is common in Thailand as well as in other southeast Asian countries such as China and Vietnam, and is therefore considered an endemic mycosis of this region.<sup>3–5</sup> Because most of the Thai patients with histoplas-

**Table 5** Chest X-ray findings of patients with histoplasmosis and penicilliosis at Srinagarind Hospital, Thailand 1996–2002.

Chest X-ray findings	Number of patients (%)	
	Histoplasmosis (n = 32)	Penicilliosis (n = 36)
Normal	19 (59.4)	25 (78.1)
Abnormal	13 (40.6)	11 (21.9)
Alveolar/patchy infiltration	2 (6.2)	2 (6.2)
Interstitial infiltration	7 (21.9)	5 (15.6)
Mixed alveolar/interstitial infiltration	0 (0.0)	1 (3.1)
Miliary infiltration	2 (6.2)	1 (3.1)
Pleural effusion	1 (3.1)	3 (9.4)
Cavitation	1 (3.1)	1 (3.1)

mosis had no history of travel to the endemic areas mentioned above, *Histoplasma capsulatum* may also be endemic to this region.

Reports from before the AIDS era revealed that histoplasmosis and penicilliosis could occur in both immunocompetent and immunocompromised patients and presented as prolonged fever, mucocutaneous ulcers or pneumonia.<sup>1,3</sup> In this study, all but one of the patients had underlying diseases, mostly HIV infection (Table 1). Almost all patients had dissemination but one patient with systemic lupus erythematosus had localized skin infection with histoplasmosis.

In this study, most of the clinical presentations of the histoplasmosis group were the same as those of the penicilliosis group (Table 1). However, abdominal pain was more common in the latter whereas hypotension and lymphadenopathy were more common in the former. Adrenal gland involvement was occasionally reported in histoplasmosis<sup>1,9,10</sup> and might have caused hypotension in some of the reported cases.

Skin lesions in the histoplasmosis group were less common than in the penicilliosis group (37.5% versus 52.8%) but not statistically different (Table 2). Wheat et al.<sup>2</sup> reported skin lesions in only 1.4% of AIDS cases with histoplasmosis, whereas Cohen et al.<sup>11</sup> reported a figure of 10.8%. Supparatpinyo et al.<sup>4</sup> reported that 71% of *P. marneffe* cases in AIDS patients had skin lesions, of which 87% were umbilicated papules. In this study erythematous plaques were most commonly found in the histoplasmosis group (15.6%) whereas umbilicated papules were more common in penicilliosis (33.3%). However, no single type of skin lesion is pathognomonic for either infection.

Most laboratory findings were similar for both infections except hyperbilirubinemia, which was more common in the penicilliosis group (Table 3).

All cases had an initial diagnosis by positive staining of discharge or by bone marrow examination before the positive culture results (Table 4). This reflects high fungal burden due to severe immunosuppression due to underlying diseases or their treatments. The characteristic morphology of *Histoplasma capsulatum* is oval or round budding yeasts intracellularly and extracellularly, differing from *Penicillium marneffe*, which are sausage-shaped yeasts with a central clear septum, resembling cells undergoing binary fission. As the organisms may cluster and be overcrowded in tissues it may not be possible to differentiate them correctly by morphology alone. In addition, *Histoplasma capsulatum* and *Penicillium marneffe* infections can occur as mixed infections together or with *Cryptococcus neoformans*,<sup>12</sup> and therefore require culture to confirm the diagnosis. Hemocultures were not helpful in

histoplasmosis by contrast with those of penicilliosis, which were positive in half the patients in this study (Table 4). The characteristics of colonies of *Histoplasma capsulatum* in fungal media may also be used for rapid differentiation from those of *Penicillium marneffe* because the former are white while the latter are red.

In this series, abnormal chest X-ray findings were more common in the histoplasmosis group (Table 5). Interstitial infiltration was the most common finding. Cohen et al.<sup>11</sup> reported that 81% of HIV-infected patients with disseminated histoplasmosis and skin lesions had an abnormal chest X-ray.

The recommended therapy of both fungi is the same: amphotericin B 0.7 mg/kg/day for two weeks, followed by itraconazole 400 mg/day for at least 10–12 weeks. Because of frequent relapses of these fungal infections in HIV-infected patients, lifelong maintenance of itraconazole of at least 200 mg/day is recommended.<sup>13–15</sup>

The prognosis of both fungal infections in this study was good. In-hospital mortality in the histoplasmosis group was the same as that of the penicilliosis group (10% versus 14.7%,  $P = 0.56$ ). No relapse of either infection occurred during long-term itraconazole therapy in HIV-infected patients. This result supports the need for secondary prophylaxis of these infections in HIV-infected patients.

In conclusion, histoplasmosis and penicilliosis had similar clinical presentations, laboratory findings and chest X-ray abnormalities, although some features may be more common than others. Response to treatment was good with low in-hospital mortality. No relapse occurred in the HIV-infected patients who had itraconazole as long-term therapy. Therefore, itraconazole is recommended as secondary prophylaxis in HIV-infected patients who have histoplasmosis or penicilliosis.

*Conflict of interest:* No conflicting interest to declare.

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