

Clinical Characteristics of Histoplasmosis in Siriraj Hospital

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Background: Histoplasmosis is a rare infectious disease caused by *Histoplasma capsulatum* (*H. capsulatum*), a dimorphic fungus. Histoplasmosis is not endemic to Thailand. Cases of histoplasmosis are sporadic and mostly associated with HIV disease. Clinical characteristics and treatment outcomes of histoplasmosis in Thai patients have not been well described.

Objective: To investigate the clinical characteristics and outcomes of patients with histoplasmosis at Siriraj Hospital in Bangkok, Thailand

Material and Method: This retrospective investigation studied adult patients with histoplasmosis who attended Siriraj Hospital for treatment between 2002 and 2012 (11 years). Clinical characteristics, microbiological data, and treatment outcomes were analyzed.

Results: Fifty-seven patients were included in the study. Twenty-one (37%) were culture-proven, 37 (64.9%) were male, and mean age was 37 years. Fifty-four (95%) patients had co-morbid diseases, of which HIV infection was the most common (85%), followed by autoimmune diseases. Mean CD4 count among HIV-infected patients was 40 (range: 1-320) cells/mm³. The most common clinical syndrome of histoplasmosis was progressive disseminated histoplasmosis (PDH) (86%), followed by chronic non-cavitary histoplasmosis (7%), and fungal synovitis (5%). Organ involvement included lungs (38%), oral cavity (4%), adrenal gland (2%), and heart valve (2%). Bone and joint infection was found in three patients, all of which were HIV-negative. Common clinical manifestations were fever (84%), weight loss (88%), anemia (63%), jaundice (16%), hepatomegaly (38%), splenomegaly (18%), lymphadenopathy (41%), and molluscum-like skin lesions (30%). Chest radiography was abnormal in 54% of patients, with 65% of those having bilateral pulmonary lesions. Interstitial infiltration was the most common radiographic finding (42%), followed by perihilar adenopathy (19%) and cavitary lesion (16%). Microscopic examination was positive for yeast-like organism in bone marrow and skin in 66% and 89% of patients, respectively. Budding yeasts were detected in all biopsied tissues obtained from oral lesions, synovium, and adrenal gland. Fungal cultures were positive from bone marrow, skin, and blood in 20%, 17%, and 5% of patients, respectively. All adrenal glands and heart valve vegetations sent for culture were positive. Fifty-one patients received amphotericin B deoxycholate followed by itraconazole, with clinical cure achieved in 86%. Survival rates at 6- and 12-month were 88% and 75%, respectively.

Conclusion: PDH is the most common syndrome of histoplasmosis in Siriraj Hospital. Skin and bone marrow study are the most useful investigations for diagnosis. Effective treatment includes amphotericin B, followed by oral itraconazole.

Keywords: Dimorphic fungi, Histoplasmosis, *Histoplasma capsulatum*, Invasive fungal infection

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Histoplasmosis is a rare infectious disease that is caused by *Histoplasma capsulatum*, a dimorphic fungus. *H. capsulatum* can infect both immunocompetent and immunocompromised individuals, especially those with HIV infection. There are four clinical syndromes of histoplasmosis, including acute pulmonary histoplasmosis, chronic cavitary histoplasmosis, chronic non-cavitary histoplasmosis, and progressive

disseminated histoplasmosis (PDH)^(1,2). Histoplasmosis-endemic regions include North, Central, and South America, Africa, Asia, and the central river valleys in the Midwestern and South-Central United States; areas from which approximately 250,000 individuals are infected annually^(1,3,4). Histoplasmosis can be transmitted through inhalation of spores (conidia) from soil that is possibly contaminated with bat guano or bird droppings; however, histoplasmosis is not transmitted directly from person to person^(1,5,6). Histoplasmosis is not endemic to Thailand. As such, cases of histoplasmosis are sporadic, with most being associated with HIV infection. Estimated prevalence of histoplasmosis in Thailand is 0.3 to 1.0% in HIV-positive patients^(6,7). The first case of histoplasmosis

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in Thailand was reported by Thep-husdin (1961) in a 16-year-old Thai male presented with generalized lymphadenopathy⁽⁸⁾. Epidemiology of serological response to histoplasmin antigen has been studied in Thai population and it revealed positive reactions in 2.59 to 28.59%, depending on regions⁽⁹⁾. However, clinical characteristics and treatment outcomes of histoplasmosis in Thai patients have not been well described.

Material and Method

A retrospective analysis was conducted of all patients diagnosed with histoplasmosis at Siriraj Hospital during the 11-year study period (January 2002 to December 2012). Patients were identified by International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) medical classifications list. A search of the Siriraj Hospital database for ICD-10 code B39 (histoplasmosis) was conducted, from which 57 patients diagnosed as histoplasmosis were identified. All 57 patients were aged 15 years or more.

Patient hospital records were systematically reviewed using a standardized protocol to assess patient demographic and clinical features, including age, gender, underlying diseases, symptoms, signs, diagnosis, chest radiographic findings, laboratory tests, and microbiological and pathological findings.

Statistical analysis

Data were presented as mean, median, and range for quantitative variables and frequency and percentage for qualitative variables. All statistical analysis was performed using SPSS Statistics version 18.0 (SPSS, Inc., Chicago, IL, USA).

Results

Fifty-seven histoplasmosis patients were enrolled. Thirty-seven (65%) patients were male, mean age of all subjects was 37 years (range: 17-71), and mean body weight was 50.7 kg. Baseline demographic and clinical features, including underlying diseases, are summarized in Table 1. Fifty-four (94.7%) patients had underlying diseases, of which 46 (80%) had HIV infection. Only three patients had no underlying disease. In patients with HIV infection, mean CD4 count was 40 (range: 1-320) cells/mm³. Baseline characteristics in patients with and without HIV infection were similar.

Clinical manifestations are summarized in Table 2. The most common symptom was weight loss

Table 1. Baseline characteristics of 57 patients with histoplasmosis

Baseline characteristics	Patients	Percent
Male gender	37	64.9
Region of residence in Thailand		
Central	39	68.5
South	7	12.2
Northeast	6	10.5
East	4	7.0
North	1	1.8
Occupation		
Labor	31	54.4
Officer	9	15.8
Sales/business	8	14.0
Agriculture	3	5.3
House wife	3	5.3
Student	2	3.5
Unemployed	1	1.8
Underlying disease	54	94.7
HIV infection	46	80.7
Congenital CD4 deficiency	2	3.5
SLE with RA	1	1.8
SLE	1	1.8
Nephrotic syndrome	1	1.8
Mitral valve stenosis	1	1.8
Hypertension	1	1.8
Acute myeloid leukemia	1	1.8
No underlying disease	3	5.3

SLE = systemic lupus erythematosus; RA = rheumatoid arthritis

Table 2. Clinical manifestations in 57 patients with histoplasmosis

Clinical manifestations	Patients	Percent
Weight loss	50	87.7
Fever	48	84.2
Anemia	35	61.4
Gastrointestinal system		
Hepatomegaly	21	37.5
Diarrhea	16	28.1
Abdominal pain	11	19.3
Splenomegaly	10	17.9
Jaundice	9	16.1
Respiratory system		
Cough	26	46.4
Hemoptysis	3	5.3
Lymphadenopathy	23	41.0
Skin lesions	18	31.1
Umbilicated papules	17	29.8
Ulcer	1	1.8
Oral mass	2	3.6
Other		
Weakness	5	8.9
Headache	4	7.1
Hypotension	3	5.3

Table 3. Baseline laboratory findings in 57 patients with histoplasmosis

Investigations	Median	Interquartile range
Hemoglobin (g/dL)	10.0	8.5-11.4
Hematocrit (%)	30.0	23.7-34.1
White blood cell (cell/mm ³)	5,550.0	3,250.0-8,705.0
Absolute neutrophil count (cell/mm ³)	3,893.5	2,274.3-6,097.5
Platelet (cell/mm ³)	149,000.0	79,750.0-308,205.0
Albumin (g/dL)	2.8	2.1-3.5
Aspartate transaminase (IU/L)	64.0	30.0-144.0
Alanine transaminase (IU/L)	35.0	15.5-81.0
Alkaline phosphatase (IU/L)	152.0	93.5-516.3
Total bilirubin (IU/L)	0.6	0.3-2.4
Direct bilirubin (IU/L)	0.2	0.1-1.0
Blood urea nitrogen (mg/dL)	13.5	10.0-20.0
Creatinine (mg/dL)	0.8	0.7-1.1

(88%), followed by fever (84%), and anemia (61%). Common respiratory manifestations included cough (46.4%) and hemoptysis (5.3%). Lymphadenopathy was found in 41%. Cutaneous manifestations mostly presented as umbilicated papules (29.8%). Hepatomegaly was found in 37.5%.

Laboratory findings are summarized in Table 3. Chest radiography (CXR) was performed in all patients, with abnormal CXR found in 31 (54.4%). The most common abnormal CXR finding was interstitial infiltration (13 patients), as shown in Table 4.

PDH was diagnosed in 49 patients (84.2%), followed by chronic non-cavitary histoplasmosis in four patients (7%), chronic histoplasma arthritis in three patients (5.2%), and infective endocarditis in one patient (2%). All patients with chronic non-cavitary histoplasmosis, chronic histoplasma arthritis, adrenal histoplasmosis, and infective endocarditis were cured. All three patients with chronic histoplasma arthritis were non-HIV patients.

Fifty-four of 57 patients (94.7%) were diagnosed by microscopic examination. Diagnosis in 21 patients (36.8%) was culture-proven. Thirty-five patients underwent bone marrow study, seven of which were culture-positive. Microscopic examination revealed *H. capsulatum* in bone marrow in 23 of 35 patients (65.7%). Skin biopsy and scrape yielded only 16.7% for fungal culture, but 88.9% exhibited the *H. capsulatum* organisms by microscopic examination (Table 5).

Table 4. Chest radiographic findings in 57 patients with histoplasmosis

Findings	Patients	Percent
Abnormal chest radiograph	31	54.5
Unilateral: right site	10	17.5
Unilateral: left site	1	1.8
Bilateral	20	64.5
Finding		
Interstitial infiltration	13	41.9
Hilar adenopathy	6	19.4
Alveolar infiltration	6	19.4
Cavitation	5	16.1
Pulmonary nodule	5	16.1
Pleural effusion	2	6.5

Table 5. Microscopic examination and culture of clinical specimens in 57 patients with histoplasmosis

Specimen	Number	Positive result			
		Microscopic examination		Culture	
		Patients	%	Patients	%
Bone marrow	35	23	66	7	20
Skin scrape/biopsy	18	16	89	3	17
Lymph node	23	11	48	2	9
Bronchial biopsy lavage	5	5	100	1	20
Synovial tissue	3	3	100	1	33
Nasopharynx	2	2	100	2	100
Oral lesion	2	2	100	1	50
Sputum	26	1	4	1	4
Pleural fluid	2	1	50	2	100
Cerebrospinal fluid	1	1	100	1	100
Adrenal gland	1	1	100	1	100
Gingival	1	1	100	0	0
Blood	57	0	0	3	5.3

All 57 patients received treatment. Fifty-one patients received induction treatment with amphotericin B, followed by itraconazole. Six patients received only itraconazole without amphotericin B for the whole course of treatment. Six patients died while being treated with amphotericin B. Successful treatment with cure was achieved in 88%. Mortality rate among histoplasmosis patients in our study was 12%. The seven patients who died were all diagnosed as progressive disseminated disease.

Discussion

Histoplasmosis is an opportunistic fungal infection in AIDS patients. It is endemic in certain parts

of the world, including South, Central, and North America, (including the Ohio and Mississippi Valleys of the United States), Africa, and Asia⁽³⁾. Histoplasmosis is rarely found in Thailand.

Previous studies from Khon Kaen Hospital, King Chulalongkorn Memorial Hospital, and Chonburi Hospital compared clinical features, laboratory findings, and outcomes of patients with histoplasmosis and penicilliosis^(5,7). From those studies, the most common clinical presentations in patients in the histoplasmosis group included fever, anemia, weight loss, lymphadenopathy, hepatomegaly, cough, and diarrhea. Most of histoplasmosis patients in the present study had HIV infection, with common clinical presentations that included weight loss, fever, anemia, lymphadenopathy, cough, hepatomegaly, and diarrhea, all of which were similar to the previous studies^(5,7). Skin lesions in histoplasmosis were found in 17 to 37.5% in the previous studies^(5,7). In this study, skin lesions were noted in 18/57 (31.6%), with umbilicated papules being the most common type. This differed from previous studies, from which plaque, papules, and ulcer were reported as being common. Hypotension was found in three patients (5.2%), compared with 37.5% and 14% in the two previous studies, respectively^(5,7). Adrenal involvement was found in one patient. Infective endocarditis was also found in only one patient, which represents the first case reported in Thailand⁽¹⁰⁾. Abnormal chest radiographs were found in 54.5% of patients in our study, with interstitial infiltration being the most common finding, similar to previous study⁽⁵⁾.

The rate of positive fungal culture was 38% in the study from King Chulalongkorn Memorial Hospital and Chonburi Hospital, which is similar to the finding from our study. In this study, cultures were positive for histoplasmosis in 21 of 57 patients (36.5%), which is the limitation of this study. *H. capsulatum* sometimes resembles *Talaromyces (Penicillium) marneffeii (T. marneffeii)*, which makes diagnosis of histoplasmosis by microscopic examination difficult. *T. marneffeii* exhibits binary fission or a central clear septum, whereas *H. capsulatum* displays intracellular and extracellular oval budding yeasts^(7,11,12). In this study, however, we found the causative organism likely to be isolated from bone marrow specimens.

In conclusion, PDH is the most common syndrome of histoplasmosis in Siriraj Hospital. Skin and bone marrow studies are the most useful investigations for diagnosis. Effective treatment includes amphotericin B, followed by oral itraconazole.

What is already known on this topic?

Histoplasmosis patients in Thailand most often present as chronic progressive disseminated disease, with fever, weight loss, and anemia being the most common features.

What this study adds?

Bone marrow study and skin scrape/biopsy produced a high yield in diagnosis of histoplasmosis. Considering the availability, affordability, and conventional nature of these procedures, bone marrow study and skin scrape are recommended in patients suspected of having histoplasmosis.

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Potential conflicts of interest

None.

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ลักษณะทางคลินิกของผู้ป่วยโรคฮิสโตพลาสโมซิสในโรงพยาบาลศิริราช

ปณิบุญย์ วงศ์พรหมเมฆ, เมธี ชยะกุลศิริ

ภูมิหลัง: โรคฮิสโตพลาสโมซิส เป็นโรคติดเชื้อที่เกิดจากราเชื้อ *Histoplasma capsulatum* ซึ่งประเทศไทยไม่ใช่ถิ่นระบาด จึงพบการติดเชื้อน้อย การติดเชื้อส่วนใหญ่สัมพันธ์กับการติดเชื้อเอชไอวี การศึกษาลักษณะทางคลินิกและผลการรักษาในประเทศไทยยังมีน้อย

วัตถุประสงค์: เพื่อศึกษาลักษณะทางคลินิกของผู้ป่วยโรคฮิสโตพลาสโมซิสในโรงพยาบาลศิริราช

วัสดุและวิธีการ: การศึกษาย้อนหลังโดยรวบรวมข้อมูลจากผู้ป่วยที่ติดเชื้อฮิสโตพลาสมาตั้งแต่วันที่ 1 มกราคม พ.ศ. 2545 ถึง 31 ธันวาคม พ.ศ. 2555 (11 ปี) โดยเก็บข้อมูลลักษณะทางคลินิกของผู้ป่วยรวมถึงข้อมูลทางจุลชีววิทยาเพื่อใช้ในการวิเคราะห์

ผลการศึกษา: ผู้ป่วยจำนวนทั้งหมด 57 ราย เป็นผู้ป่วยที่เพาะเชื้อขึ้น 21 ราย (ร้อยละ 44) ผู้ป่วยชาย 37 ราย (ร้อยละ 65) อายุเฉลี่ย 37 ปี ผู้ป่วย 54 ราย (ร้อยละ 95) มีโรคร่วมซึ่งส่วนใหญ่เป็นโรคเอดส์ร้อยละ 80 รองลงมาคือ โรคแพ้ภูมิตนเอง ในผู้ติดเชื้อเอชไอวี พบว่า ค่าเฉลี่ยเม็ดเลือดขาวซีดีโฟร์ คือ $40 (1-320) \text{ cells/mm}^3$ กลุ่มอาการของโรคฮิสโตพลาสโมซิสที่พบบ่อย คือ กลุ่มอาการแพร่กระจาย (ร้อยละ 86) การติดเชื้อในปอด (ร้อยละ 7) การติดเชื้อที่ข้อ (ร้อยละ 5) อวัยวะติดเชื้อที่พบบ่อยคือระบบทางเดินหายใจ (ร้อยละ 38) ฟื่นในปาก (ร้อยละ 4) ต่อมทอนซิล (ร้อยละ 2) ลิ้นหัวใจ (ร้อยละ 2) โดยพบว่าโรคฮิสโตพลาสโมซิสที่ข้อทั้งสามคน พบในผู้ป่วยที่ไม่มีโรคเอดส์ อาการแสดงที่พบบ่อยคือ ไข้ (ร้อยละ 84) น้ำหนักลด (ร้อยละ 88) ซีด (ร้อยละ 63) ตับโต (ร้อยละ 38) ม้ามโต (ร้อยละ 18) เหลือง (ร้อยละ 16) ต่อมทอนซิลโต (ร้อยละ 41) ฟื่นบวมตรงกลาง (ร้อยละ 30) การตรวจภาพรังสีทรวงอก พบความผิดปกติร้อยละ 54 โดยร้อยละ 65 พบความผิดปกติทั้งสองข้าง พบความผิดปกติแบบ *interstitial infiltration* ร้อยละ 42 ต่อมทอนซิลโตที่ขั้วปอดร้อยละ 19 ก้อนในปอดร้อยละ 16 การตรวจทางพยาธิวิทยาพบเชื้อก่อโรคจากไขกระดูก ร้อยละ 66 จากผิวหนังร้อยละ 89 รอยโรคที่ปาก ข้อ และต่อมทอนซิลทั้งหมดตรวจพบเชื้อก่อโรค ผลเพาะเชื้อให้ผลบวกจากไขกระดูกร้อยละ 20 ผิวหนังร้อยละ 17 เลือดร้อยละ 5 ต่อมทอนซิลและลิ้นหัวใจร้อยละ 100 ผู้ป่วย 51 ราย ได้เริ่มการรักษาด้วย *amphotericin B* รักษาต่อด้วย *itraconazole* 49 ราย ผลการรักษาหายร้อยละ 88 และเสียชีวิตร้อยละ 12

สรุป: โรคฮิสโตพลาสโมซิสชนิดแพร่กระจายพบมากที่สุดในผู้ป่วยโรคติดเชื้อฮิสโตพลาสมาในโรงพยาบาลศิริราช การตรวจชิ้นเนื้อ ผิวหนัง หรือ ตรวจไขกระดูกช่วยในการวินิจฉัยโรค และการรักษาที่ได้ประสิทธิภาพคือ การรักษาด้วย *amphotericin B* และรักษาต่อด้วย *itraconazole*