CLINICAL CHARACTERISTICS OF HISTOPLASMOSIS PATIENTS TREATED AT MAHARAJ NAKORN CHIANG MAI HOSPITAL, THAILAND

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Abstract. Histoplasmosis, caused by *Histoplasma capsulatum*, is not endemic in Thailand. In this study we aimed to describe the characteristics of patients with histoplasmosis in northern Thailand, treated at Maharaj Nakorn Chiang Mai Hospital, in order to better understand the epidemiology of this disease in this patient population. We retrospectively reviewed the medical records of patients treated at Maharaj Nakorn Chiang Mai Hospital, Chiang Mai, Thailand for histoplasmosis during January 2009-February 2019 and recorded the following data: patient demographics, clinical characteristics, microbiological data and treatment outcomes. A total of 49 subjects were included in the study; 34 (69%) males. The mean (±standard deviation) age of study subjects was 51 (±16) (range: 16-87) years. The most common underlying disease was human immunodeficiency virus (HIV) infection (*n* = 16, 33%), followed by adult-onset immunodeficiency due to anti-interferon-γ autoantibodies (anti-IFN- γAAb) (*n* = 9, 18%) and diabetes mellitus (*n* = 4, 8%). The median (interquartile range; IQR) CD4 cell count among HIV-infected patients was 21 (15-39) cells/mm^3. The most common presenting symptoms were fever (*n* = 28, 57%), weight loss (*n* = 14, 29%), anemia (*n* = 14, 29%), cough (*n* = 9, 18%) and lymphadenopathy (*n* = 9, 18%). Patients with HIV-infection were younger, more likely to have lymphadenopathy, less likely to have pulmonary, bone or joint infections and more likely to have disseminated infection than patients without HIV-infection. The most common clinical presentation among those with HIV infection was disseminated histoplasmosis (*n* = 11, 69%) and among those without HIV infection was pulmonary histoplasmosis (*n* = 9, 28%). Fifty-five patients (93%) received treatment. The median (IQR) duration of treatment was 16 (12-52) weeks. The mortality rate was 6% (*n* = 3).

In summary, most of the histoplasmosis patients in our study were male, middle to older aged, had HIV infection and had disseminated histoplasmosis. Among those without HIV the most common clinical presentation was pulmonary histoplasmosis and the most common underlying condition was anti-IFN- γAAb. We conclude given the uncommon incidence of histoplasmosis in Thailand, physicians caring for patients with these associated factors in the study area should keep a strong index of suspicion for histoplasmosis if they present with these symptoms. Further studies are needed to determine what the incidence of histoplasmosis is in other parts of Thailand and Southeast Asia.

Keywords: histoplasmosis, *Histoplasma capsulatum*, epidemiology

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INTRODUCTION

Histoplasmosis, caused by *Histoplasma capsulatum*, a dimorphic fungus found in the environment, is endemic in parts of Africa, Australia and Central and South America (Adenis *et al*, 2014; McLeod *et al*, 2011; Chakrabarti and Slavin, 2011). It can cause disease in both immunocompetent and immunocompromised patients but the risk for disseminated infection is 10 times higher among immunocompromised patients (Sathapatayavongs *et al*, 1983), particularly among those with defects in cell-mediated immunity (Horwath *et al*, 2015; Deepe, 2005). It is not a common opportunistic fungal infection in people living with HIV/AIDS (PLWHA) in Thailand (Wongprommek and Chayakulkeeree, 2016; Mootsikapun and Srikulbutr, 2006; Rangwala *et al*, 2012; Chayakulkeeree and Denning, 2017). HIV infection has been reported to be the most common underlying disease among patients with histoplasmosis (Wongprommek and Chayakulkeeree, 2016; Mootsikapun and Srikulbutr, 2006; Rangwala *et al*, 2012).

In our study, we aimed to determine the clinical characteristics of patients diagnosed with histoplasmosis in northern Thailand and treated at our hospital in order to better understand the epidemiology of this disease in our patient population in northern Thailand.

MATERIALS AND METHODS

Study design

We retrospectively reviewed the medical records of all the subjects aged ≥15 years diagnosed with histoplasmosis treated at Maharaj Nakorn Chiang Mai Hospital Chiang Mai University, Thailand during January 2009-February 2019 and recorded the following data: demographics, clinical manifestations, diagnoses, laboratory findings, microbiological and pathological findings, treatments and outcomes.

Statistical analysis

We used numbers and percentages, means and standard deviations (SD) (%) and medians and interquartile ranges to describe and evaluate the data where appropriate. We used Chi-squares, Fisher's Exact tests, Student t-tests, and Mann-Whitney U tests, where appropriate, to compare groups. A *p*-value of <0.05 was considered statistically significant. All statistical analyses were conducted using Stata, version 14.0 (Stata Corporation, College Station, TX).

Ethical consideration

This study was approved by the Ethics Review Board of the Faculty of Medicine, Chiang Mai University (STUDY CODE: MED-2562-06352).

RESULTS

Forty-nine patients were included in this study, 34 (69%) males. The mean (±SD) age of all study subjects was 51 (±16) (range: 16-87) years, among those with HIV infection was 35 (±11) (range: 16-57) years and among those without HIV infection was 59 (±12) (range: 29-87) years. The mean age of subjects with HIV infection was significantly lower than those without HIV infection ($p<0.001$). Forty patients (82%) had an underlying disease, with HIV infection being the most common (16 of 40, 40%), followed by adult-onset immunodeficiency caused by anti-interferon-γ autoantibody (anti-IFN- γAAb) (7 of 40, 18%), diabetes mellitus (4 of 40, 10%), hypertension (3 of 40, 8%), being status post-renal transplant (2 of 40, 5%), having systemic lupus erythematosus (SLE) (2 of 40, 5%), having psoriatic

arthritis (1 of 40, 3%), having diffuse systemic sclerosis (1 of 40, 3%), having adrenal insufficiency (1 of 40, 3%), having dyslipidemia (1 of 40, 3%), having cerebrovascular disease (1 of 40, 3%) and having cirrhosis (1 of 40, 3%). The median CD4 count among subjects with HIV infection was 21 (range: 15-39) cells/mm^3.

The most common presenting symptoms were fever (57%), weight loss (29%), anemia (29%), cough (18%) and lymphadenopathy (18%) (Table 1).

Table 1

Clinical manifestations of study subjects (N = 49)

Clinical manifestation	Frequency *n* (%)
Fever	28 (57)
Weight loss	14 (29)
Anemia	14 (29)
Cough	9 (18)
Lymphadenopathy	9 (18)
Umbilicated papules	5 (10)
Diarrhea	5 (10)
Oral mass	5 (10)
Abdominal pain	4 (8)
Hepatomegaly	3 (6)
Oral ulcer	2 (4)
Arthritis	2 (4)
Splenomegaly	1 (2)
Hemoptysis	1 (2)
Dyspnea	1 (2)
Wrist mass	1 (2)
Epistaxis	1 (2)
Odynophagia	1 (2)

The laboratory results among study subjects were as follows: the median (interquartile range; IQR) hemoglobin was 11 (9.0-13) g/dl, the median white blood cell count was 6,300 (4,820-9,770) cells/ mm^3, the median platelet count was 194,000 (108,000-280,000) cells/ mm^3, the median albumin level was 3.4 (2.9-3.9) g/dl, the median alanine transaminase level was 27 (18-40) IU/l, the median alkaline phosphatase level was 124 (74-208) IU/l and the median creatinine level was 1.0 (0.8-1.4) mg/dl.

The biopsied tissues containing *Histoplasma capsulatum* were the skin, synovium, nasopharynx, supraglottic lesions, sclera and adrenal gland. *Histoplasma capsulatum* grew from the synovium, oral lesions, adrenal gland and lymph nodes in 50%, 33%, 33% and 20% of subjects, respectively (Table 2).

The most common clinical diagnosis was disseminated histoplasmosis (n = 16, 33%), followed by pulmonary histoplasmosis (n = 11, 22%) bilateral adrenal histoplasmosis (n = 7, 14%), histoplasma osteomyelitis (n = 5, 10%), cutaneous histoplasmosis (n = 4, 8%), histoplasma lymphadenitis (n = 3, 6%), histoplasma scleritis (n = 1, 2%), nasal cavity histoplasmosis (n = 1, 2%) and tongue histoplasmosis (n = 1, 2%).

The most common clinical manifestation of histoplasmosis among subjects with HIV infection was disseminated histoplasmosis and among subjects without HIV infection was pulmonary histoplasmosis. These differences were significant (p<0.001) (Table 3).

Forty-eight subjects received treatment and one refused. Twenty-four subjects (50%) received amphotericin B followed by itraconazole and 21 subjects (44%) received itraconazole only. The median (IQR) duration of treatment was 16 (12-52) weeks. Thirty-seven subjects (76%) were cured and 3 (6%) died. The duration of treatment among subjects without HIV infection was significantly longer than among subjects with HIV infection (p = 0.001) (Table 4).

DISCUSSION

Disseminated histoplasmosis is a serious opportunistic infection in patients with acquired immunodeficiency syndrome (AIDS) (Wongprommek and Chayakulkeeree, 2016). This disease is

Table 2

Microscopy and culture results among study subjects (N=49)

Specimens	Microscopy Number detected/number sent (%)	Culture positive for *Histoplasma capsulatum* Number detected/number sent (%)
Bone marrow	11/17 (65)	2/16 (13)
Skin scraping/ biopsy	5/5 (100)	1/5 (20)
Lymph node	3/6 (50)	1/5 (20)
Bronchial biopsy/bronchoalveolar lavage	9/13 (69)	2/13 (15)
Lung biopsy	2/2 (100)	N/A
Synovial tissue	2/2 (100)	1/2 (50)
Nasopharynx	1/1 (100)	N/A
Oral lesion	4/5 (80)	1/3 (33)
Supraglottic lesion	1/1 (100)	N/A
Sputum	0/7 (0)	1/7 (14)
Cerebrospinal fluid	0/1 (0)	0/1 (0)
Adrenal gland	7/7 (100)	1/3 (33)
Sclera	1/1 (100)	0/1 (0)
Blood	N/A	1/31 (3)

N/A: not applicable

Table 3

Characteristics of study subjects by HIV serostatus

Characteristic	HIV negative (N = 32)	HIV positive (N = 16)	*p*-value
Male, *n* (%)	21 (66)	12 (75)	0.509
Age in years, mean ± SD	59 ± 11	35 ± 11	<0.001
Site of infection, *n* (%)			<0.001
Bone or joint	5 (16)	0	
Skin or soft tissue	3 (9)	1 (6)	
Sclera	1 (3)	0	
Nasal cavity	1 (3)	0	
Tongue	1 (3)	0	
Lung	9 (28)	1 (6)	
Lymph node	0	3 (19)	
Disseminated histoplasmosis	5 (16)	11 (69)	<0.001
Bilateral adrenal histoplasmosis	7 (22)	0	<0.079

Note: One patient denied checking HIV serostatus, therefore; the total number of participants in this Table is 48 comprising 32 HIV negative and 16 HIV positive.
HIV: human immunodeficiency virus; SD: standard deviation

uncommon in Thailand, but there are reported cases (Wongprommek and Chayakulkeeree, 2016; Mootsikapun and Srikulbutr, 2006; Rangwala *et al*, 2012). The majority of patients in the above studies from Thailand who had histoplasmosis had HIV infection, but in our study less than half of the subjects had HIV infection. This difference could be because our study is more recent and there is better HIV diagnosis and care now than in the past, leading to fewer HIV patients with low CD4 counts now than in the past (INSIGHT START Study Group, 2015; TEMPRANO ANRS 12136 Study Group, 2015). However, the number

Table 4

Treatments and outcomes among study subjects

Variable	HIV negative (N = 32)	HIV positive (N = 16)	*p*-value
Treatment, *n* (%)			0.248
Amphotericin B followed by itraconazole	14 (44)	10 (67)	
Itraconazole only	16 (50)	4 (27)	
Amphotericin B only	2 (6)	1 (7)	
Duration of treatment in weeks, median (IQR)	32 (14-52)	12 (2-14)	0.001
Outcome, *n* (%)			0.359
Cured	28 (88)	13 (81)	
Died	2 (6)	1 (6)	
Lost to follow up	2 (6)	1 (6)	
Refused treatment	0 (0)	1 (6)	

Note: One patient denied checking HIV serostatus, therefore; the total number of participants in this Table is 48 comprising 32 HIV negative and 16 HIV positive.
HIV: human immunodeficiency virus; IQR: interquartile range

of patients with immunosuppression due to medical treatment has increased (Briggs, 1991). The prevalence of adult-onset immunodeficiency due to anti-IFN- γAAb has been increasing in Asia (Angkasekwinai *et al*, 2019; Browne *et al*, 2012; Wongkulab *et al*, 2013). As seen in our study, this is associated with a higher risk of contracting histoplasmosis.

The clinical manifestations of disseminated histoplasmosis seen in our study included fever, weight loss, anemia and diarrhea, similar to those reported by previous studies (Wongprommek and Chayakulkeeree, 2016; Mootsikapun and Srikulbutr, 2006). The proportion of our study subjects with umbilicated papules due to histoplasmosis of the skin

(1%) was lower than that reported in a previous similar study from Thailand (30%) (Wongprommek and Chayakulkeeree, 2016), probably because the proportion of subjects in our study who had HIV infection was less than the comparison study and patients without HIV infection are less likely to develop these skin lesions.

In our study the clinical manifestations of subjects without HIV infection (pulmonary and adrenal histoplasmosis) differed from those with HIV infection (disseminated histoplasmosis) similar to the findings of a previous study (Wheat *et al*, 2016).

The gold standard for diagnosing histoplasmosis is isolation of *Histoplasma capsulatum* from the bone marrow (72-100%), blood (23-91%), skin biopsy or scraping (100%) or lymph nodes (86-100%) (Adenis *et al*, 2014; Mootsikapun and Srikulbutr, 2006; Rangwala *et al*, 2012; Wheat *et al*, 1990). In our study subjects we had good cure rates with itraconazole with or without amphotericin B, similar to the findings of previous studies (Wongprommek and Chayakulkeeree, 2016; Mootsikapun and Srikulbutr, 2006; Wheat, 1995).

In summary, most of the study subjects were male, middle to older aged, had HIV infection and had disseminated histoplasmosis. Among those without HIV infection, the most common clinical presentation was pulmonary histoplasmosis and the most common underlying condition was anti-IFN- γAAb. We conclude given the uncommon incidence of histoplasmosis in Thailand, physicians caring for patients with these associated factors in the study area should keep a strong index of suspicion for histoplasmosis if they present with these symptoms. Further studies are needed to determine what the incidence of histoplasmosis is in other parts of Thailand and Southeast Asia.

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CONFLICT OF INTEREST DISCLOSURE

The authors declare no conflict of interest.

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