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The Review of Histoplasmosis Endemicity and Current Status in Asia

Anna Rozaliyani and Findra Setianingrum

Abstract

Histoplasmosis is a common disease among immunocompromised patients and a notable endemic disease among immunocompetent patients. Disseminated histoplasmosis in acquired immunodeficiency syndrome (AIDS) patients is mostly lethal. We conducted a literature review of histoplasmosis and histoplasmin skin test in Asia. There were around 1692 cases of histoplasmosis reported from Asian countries. India (623 cases), China (611 cases) and Thailand (234 cases) are detected as endemic areas of histoplasmosis although the complete mapping of this disease is still missing in some Asian countries. However, definite diagnosis is difficult since the symptoms frequently mimicking tuberculosis (TB), tissue samples are rarely obtained, and lacked of serology tests in Asian countries.

Keywords: histoplasmosis, Asia, epidemiology

1. Introduction

The first documented case of histoplasmosis in Asia was detected in a 7-year-old boy from Java, Indonesia, 26 years after Dr Samuel Darling described the first case of histoplasmosis [1, 2]. The differential diagnosis of the patient was visceral leishmaniasis, but the appendix, ileum and mesenteric lymph nodes showed histological evidences of histoplasmosis [2]. Randhawa reported 30 cases of histoplasmosis in 1970 from Asia [3]. India accounted for the highest number of 11 cases, followed by Indonesia (8 cases), Malaysia (4 cases), Thailand (2 cases), Singapore (2 cases), Vietnam (2 cases) and Japan (1 case) [3]. Together with the isolation of *Histoplasma capsulatum* from soil in Malaysia, it is implied that Malaysia is the endemic area of histoplasmosis [3]. Recent study documented 407 cases of histoplasmosis from Southeast Asian countries with Thailand as the leading country with 223 cases [4].

Human immunodeficiency virus (HIV) is a classical risk factor in histoplasmosis although there are a growing number of reports of histoplasmosis among other immunocompromised patients as well as immunocompetent patients in Asia [5–7]. The mortality of histoplasmosis among immunocompromised patients was 27.5%; this rate is significantly higher than the rate in immunocompetent patients (10%) [5]. Histoplasmosis was also often misdiagnosed as tuberculosis (TB) as many countries in Asia are high-burden TB countries [8–10]. The complete understanding of *Histoplasma* endemicity is crucial to enhance the awareness of clinicians in Asia to diagnose histoplasmosis. We reviewed the current status of histoplasmosis in Asia through analysis of published studies.

2. Methods

A literature search was conducted in PubMed and Google Scholar using the keywords “histoplasmosis” and “Asia”, and also the combinations of “histoplasmosis” or *Histoplasma* or “histoplasmin” with the name of each country in Asia, in February 2020. The following countries were included as part of Asia: the Philippines, Singapore, Thailand, Vietnam, Cambodia, Brunei, Indonesia, Laos, Malaysia, Myanmar, India, Bangladesh, Pakistan, Sri Lanka, Nepal, China, Turkey, Iraq, Iran, Taiwan, Lebanon, Syria, Qatar, Saudi Arabia, Kuwait, Japan and Korea.

2.1 Epidemiology of histoplasmosis in Asia

Our review of the literature produced a total of 1692 cases of histoplasmosis reported in Asia from both areas known as endemic (Indian subcontinent, China, Southeast Asia) and non-endemic (Turkey, Iraq, Iran and Taiwan). India accounted for the highest number of cases with 623 cases, followed by China (611 cases), Thailand (234 cases), Malaysia (77 cases) and Indonesia (48 cases) (**Table 1**).

The countries included in the search to not produce any indigenous cases were Lebanon, Syria, Qatar, Saudi Arabia, Kuwait, Jordan, Japan, Korea and Brunei. Other countries in Asia were considered as non-endemic areas for *Histoplasma*, but there were possibilities of imported cases of histoplasmosis [11, 12]. Imported cases were revealed based on the travel history of patients to other Asian countries such as Malaysia, Indonesia, Thailand, Singapore and China [12]. Japan and Korea

No.	Country	No. of cases	References
1	India	623	[6, 8–10, 22–59]
2	Bangladesh	27	[6, 60]
3	Pakistan	5	[6, 61]
4	Sri Lanka	4	[6, 62]
5	Nepal	5	[6]
6	Cambodia	5	[4]
7	China	611	[7, 63–72]
8	Thailand	234	[4, 73]
9	Indonesia	48	[4]
10	Laos	1	[74]
11	Myanmar	3	[75–77]
12	Singapore	21	[4]
13	Philippines	14	[4]
14	Malaysia	77	[4, 78]
15	Vietnam	6	[4, 79]
16	Turkey	2	[16, 80]
17	Iraq	2	[18]
18	Iran	2	[19, 81]
19	Taiwan	2	[12, 20]
	Total	1692	

Table 1.
Cases of histoplasmosis in Asian countries.

revealed imported cases of histoplasmosis with 100 cases and 245 cases, respectively [13–15]. There is also small portion of indigenous cases from Iraq, Iran, Turkey and Taiwan which occurred in immunocompromised patients such as patients with long-term corticosteroid therapy, history of renal transplant or genetic immunodeficiency [16–21].

2.1.1 Indian subcontinent

The histoplasmosis cases from India are based on the study from Randhawa and Gugnani who found a total of 426 cases (1954–2018) and 207 cases from the literature search (2018–2020, excluded studies cited in Randhawa and Gugnani) [6]. The trend of reporting histoplasmosis cases was notably increased in the past 2 years, which might be caused by rising of awareness of clinicians to diagnose histoplasmosis. However, whether this increase is caused by a real increased number of patients infected by *Histoplasma* in India is unclear.

The regions along the Ganga river basins such as West Bengal and Uttar Pradesh in India were considered as endemic pockets of histoplasmosis [6, 82, 83]. Histoplasmosis cases also existed from other areas in India, which included Delhi, Rajasthan, Maharashtra and Haryana [6, 84–87]. The sole evidence of environmental source of *Histoplasma* in India was the isolation of this organism from the soil from building related to bat habitats near Calcutta, part of Ganga river basins [83].

The data of human immunodeficiency virus (HIV) status were available for 136 patients from 207 histoplasmosis patients in India between 2018 and 2020 (Table 2). Histoplasmosis mostly occurred in HIV-negative patients (91%, n = 124). Only 12 patients (9%) were HIV positive in this case series. The most common manifestation in the HIV-negative patients is adrenal histoplasmosis (44%, n = 54). Other study also found HIV-negative cases outnumbered HIV-positive cases with the rate of 64% proven histoplasmosis in a retrospective study from New Delhi [42].

Adrenal histoplasmosis (44%, n = 54) was the most common manifestation of histoplasmosis among 124 histoplasmosis cases with HIV negative. A recent study reported an adequate response of antifungal therapy in adrenal histoplasmosis with the rate of 86% with a median duration of follow-up of 2.5 years [50]. However, the mortality is high (20%, 8 out of 29 patients) even among patients with completed therapy.

Type of histoplasmosis	HIV positive	Reference	HIV negative	Reference
Disseminated	0	–	29	[8, 10, 22, 23, 27, 28, 33, 38, 44, 45, 47–49, 52, 53, 55, 88]
Adrenal	0	–	54	[26, 36, 43, 50, 56]
Pulmonary	1	[10]	1	[37]
Gastrointestinal	3	[24, 35]	4	[35]
Cutaneous	0	–	2	[34, 39]
Conjunctival	1	[41]	0	–
Laryngeal	0	–	1	[29]
Oral	0	–	2	[32, 33]
Mixed organs	6	[59]	31	[59]
Total	11		124	

Table 2.
HIV status from 135 patients (2017–2020) with available data.

There were no risk factors detected in 10 patients among 29 HIV-negative patients with histoplasmosis, considering this group of patients was immuno-competent [8, 10, 23, 28, 33, 44, 45, 88]. One patient had dual infections of disseminated histoplasmosis and TB with fever, lymphadenopathy, splenomegaly and pancytopenia [23]. The patient showed a partial response to antitubercular therapy. *Histoplasma* grew from a bone marrow culture of patient proved the diagnosis of disseminated histoplasmosis. Another unusual case was the occurrence of a progressive disseminated histoplasmosis in an immunocompetent patient with prolonged fever of unknown origin [8]. CT of the thorax was normal; later, the patient developed pharyngeal ulcer and papulonodular rash that the biopsies from these lesions turned to be positive for *Histoplasma*. The most common risk factor in HIV-negative patients was diabetes (41 patients) (**Table 3**).

A review of literature from Bangladesh revealed 27 cases of histoplasmosis with the first case reported from Dhaka in 1982. Dhaka is the most common city appeared in the list with 17 cases, followed by Chittagong, Gopalganj and Mymensingh with each of the area had one case of histoplasmosis. Four patients were diagnosed outside Bangladesh and three patients had unknown location. The cases from Bangladesh were all adult males, with 15% (four patients) who had acquired immunodeficiency syndrome (AIDS). The predominance of male population with histoplasmosis was also found in many case series [42, 50, 59]. The most common type of histoplasmosis was disseminated histoplasmosis. Seven cases of adrenal histoplasmosis in HIV-negative patients were observed in the recent case series from Bangladesh [60]. Weight loss, anorexia and fever were the common symptoms. Bilateral adrenal enlargement was seen in these patients. The diagnosis of histoplasmosis was obtained from CT-guided fine needle aspiration cytology. Four patients have diabetes as their risk factor. There is no travel history outside Bangladesh in all seven patients indicating Bangladesh as a potential endemic area of *Histoplasma*. Histoplasmosis was also reported in a small number of cases from Pakistan (five patients), Sri Lanka (four cases) and Nepal (five cases).

Several studies reported the result of histoplasmin tests in India [3, 89–91]. The range of positivity was estimated between 0 and 12.3% [3, 91]. The highest rate of positivity (12.3%) was identified from a survey in Delhi, particularly in the area near the Jumna River [89]. The zero rate of positivity was obtained from Kelur, Goa, Ramgarh and Kerala [3, 90]. The positivity of histoplasmin between 12.58 and

Conditions	No. of cases	Reference
Diabetes	41	[30, 35, 47, 48, 53, 59]
Chronic granulomatous disease	2	[52, 55]
Corticosteroid therapy	3	[9, 22, 38]
Other immunosuppressive therapies	2	[22, 38]
Idiopathic CD4 lymphocytopenia	2	[27, 35]
Kidney transplant	1	[29]
TB with severe malnutrition	1	[35]
Lymphoma	1	[35]
Chronic liver disease	1	[59]
Chronic kidney disease	1	[59]
Total	55	

Table 3.
Risk factors in HIV-negative cases from 207 histoplasmosis cases (2018–2020).

13.75% was observed among 2,729 people from Bangladesh (formerly called East Pakistan) [92]. Meanwhile, all of the 575 people (healthy participants, schoolchildren and TB and leprosy patients) showed a zero rate of histoplasmin sensitivity in Pakistan [93]. Nepal reported histoplasmin positivity in the rate of 5.7% among 1336 students and prisoners [94].

2.1.2 Southeast Asia

The total number of histoplasmosis cases from Southeast Asian countries was 410 cases with 178 (43%) cases were related to HIV-positive patients. Diabetes was noted as the risk factor in histoplasmosis case among HIV-negative patients in Southeast Asia [4]. Thailand ranked one in the number of cases of histoplasmosis in Southeast Asia, followed by Malaysia based on our literature search (**Table 1**). The dominant cases from these two countries may reflect the clinical awareness and presence of active case finding of histoplasmosis especially from HIV-positive population, which lacked in most other Southeast Asian countries [4].

HIV was found in 85% of patients in the retrospective cohort study in Thailand [95]. Risk factors for histoplasmosis were not detected in three patients (5%). Progressive disseminated histoplasmosis was the most common (86%) clinical manifestation. The organs involved include the lung, oral cavity, adrenal gland and heart valve. Most of the patients (69%) were located in Central Thailand. Weight loss, fever and anemia were commonly found in patients, followed by cough, lymphadenopathy, hepatomegaly and skin lesions. *Histoplasma* were present in microscopic examination at the rate of 89% from skin biopsy and scrape, while only 16.7% of fungal culture positive for this organism from skin tissue. The mortality rate is 12%, with all deaths coming from progressive disseminated histoplasmosis.

The evidence of environmental sources of *Histoplasma* in Thailand was obtained from the soil contaminated with bat guano and chicken dropping from Chiang Mai [96]. The detection was carried out by nested PCR on 265 soil samples. Bat guano and chicken dropping were often used as fertilizers among local gardeners. This might play a role as one of the possible contacts of this organism to humans.

A retrospective study of oral histoplasmosis in Malaysians observed older age (>54) and serious systemic illness as common risk factors [97]. All cases were proven histopathologic findings of the yeast phase of *Histoplasma capsulatum*. TB and squamous cell carcinoma were the differential diagnoses in this report. However, there is no available information regarding the immune status in this study. Five (14%) patients later developed disseminated histoplasmosis. The clinical information was not available in the remaining patients whether the patients had disseminated disease or isolated oral histoplasmosis. Other histoplasmosis cases from Malaysia were reported as a single or small case series. Disseminated histoplasmosis was diagnosed in HIV-negative patients with diabetes and high exposure of bird droppings in Sarawak, Malaysia [98]. The Malaysian Medical Association published environmental control measures to replace tall trees with shorter trees and promoted the electricity and telephone cables underground to reduce bird droppings in Sarawak [99]. The areas nearby Sarawak, Sibu and Sarikei had many histoplasmosis cases possibly due to abundant exposure of bird droppings.

Most of the histoplasmosis in Indonesia was also reported as a case report or small case series. Seven HIV-positive patients with disseminated histoplasmosis were diagnosed based on the histopathologic findings in Jakarta. The study showed there is no correlation between CD4 counts with the clinical morphology and distribution of lesions [100]. The mean CD4 count was 49.8 cells/mm³. Papules, plaques, hypertrophic scars, ulcers and scales were identified dominantly in the face. Touch biopsy was used to identify histoplasmosis in 27 patients with HIV

positive in Jakarta [101]. *Histoplasma capsulatum* were detected in 10 patients (37%), suggesting this method might be suitable in the resource-limited setting to diagnose histoplasmosis.

Histoplasmin positivity in Southeast Asia varied widely across countries, ranging from 0.5% in Sarawak, Malaysia, to 86.4% in Maguee, Myanmar [4, 102–104]. Most of the studies used the induration of 5 mm or more as a sign of positive reaction. The 0.5% rate was obtained from 181 schoolchildren/hospital patients, and the 86.4% rate was observed from prisoners/prison staff. Luzon Island, Philippines, reported a histoplasmin positivity rate of 26% among 143 electric company employees [104].

2.1.3 China

The number of cases from China (611 cases) was based on the recent report from Xin et al. with most of the cases reported from Yunnan province, followed by Hunan and Hubei provinces [7]. These three regions are located along the Yangtze River flows. Other provinces that are located in the Yangtze River were identified as histoplasmosis endemic regions, including Jiangsu, Sichuan and Chongqing [63]. Among the 611 cases, 34 cases from Hunan were reviewed for clinical history. It showed 13 patients were immunocompromised with most of them (8 patients) confirmed as HIV-positive cases [7]. Twenty-one patients were considered as immunocompetent. All cases were proven with tissue biopsy with the bone marrow as the most common site of biopsy. The predominant organ involved was the lungs, oral cavities and intestines.

Pan identified 300 cases of histoplasmosis in China during 1990–2011 [63]. Traveling history was present in 195 patients. It revealed that most of the patients (91%, $n = 178$) had no history travel outside China which indicated the endemicity of histoplasmosis in China. HIV positive comprised 22% ($n = 38$) of the cases among 173 patients with clear clinical information. Around 49% ($n = 85$) patients showed no underlying disease, with most of them (89%, $n = 76$) unexpectedly diagnosed with disseminated histoplasmosis.

The histoplasmin rate in normal people with no history of travel outside China revealed the highest rate is from Jiangsu (15.1%) [105]. Hunan reported a rate of 8.9%, while Xinjiang reported a rate of only 2.1%. Another study from China revealed a rate of 35% of histoplasmin positivity from Sichuan province [106].

3. Diagnostic challenges of histoplasmosis in Asia

The diagnosis of histoplasmosis in many regions in Asia is still inadequate due to the lack of awareness of this disease. Clinical symptoms are difficult to distinguish from other lung diseases, including tuberculosis and several other diseases that require different managements. The identification of *H. capsulatum* in clinical material can be determined by several techniques, including direct fungal visualization and culture, histopathology, antibody or antigen detection and molecular-based testing. These methods have different sensitivity and specificity ranges, depending upon the methodology, clinical form of the disease and host immune status.

In Asian countries with limited facilities, the diagnosis is classically carried out by direct examination of clinical specimens. The sensitivity and specificity of direct examination by using potassium hydroxide (KOH 10%) are very low. Histopathology and cytopathology with specific fungal staining is considered another important method in diagnosing histoplasmosis, but it requires invasive procedures for obtaining specimens and needs professional expertise to identify the specific fungal elements. The histopathologic examination may achieve the highest

yield by evaluating bone marrow biopsies and respiratory specimens from disseminated histoplasmosis patients. A touch preparation analysis of the skin or skin biopsy shows the utility in diagnosing cutaneous mycoses or skin-related systemic mycoses, including disseminated histoplasmosis [101, 107]. The test is simple and suitable for rapid presumptive diagnosis, especially in HIV-infected patients.

4. Discussion

The histoplasmosis cases during the last 3 years in India were dominated with HIV-negative patients based on our literature search. This is in contrast with the period before 2018 that indicated HIV as the common comorbidity among histoplasmosis in India [6]. This may also reflect a decline of annual new HIV infections by 27% during 2010–2017 [108]. The endemic area of histoplasmosis in India (West Bengal and Uttar Pradesh) reported a decline of new HIV infection in 2010–2017, in the rate of 11% and 34%, respectively [108]. Meanwhile there are a limited number of studies from other regions in Asia regarding the HIV status of histoplasmosis.

Diabetes is the most common risk factor detected in HIV-negative histoplasmosis in India and Southeast Asia. India is the second country with the biggest burden of diabetes in the world [109]. There is an increase of diabetes population in India from 40.9 million people in 2007 to 77 million people in 2019 [109, 110]. The growing population of diabetes might contribute to the common findings of diabetes as a risk factor in histoplasmosis. Diabetes was commonly found as a predisposing factor in the mortality of adrenal histoplasmosis [50].

Histoplasmosis has the most varied presentations. The mild pulmonary histoplasmosis may occasionally get complicated by pericarditis or rheumatologic manifestation. After heavy exposure to *H. capsulatum* spores in the soil contaminated with bird or bat droppings, patients may present with severe acute pulmonary histoplasmosis needing hospitalization. Patients with underlying obstructive pulmonary disease may exhibit progressive chronic pulmonary histoplasmosis. Immunosuppressed patients usually present with progressive disseminated histoplasmosis, which manifests as either a chronic or acute disease. The diagnosis of *Histoplasma* which are based on tissue histopathology should be carefully evaluated as the overlap morphology of *H. capsulatum* and *Penicillium marneffe*, particularly because *P. marneffe* also endemic in certain areas in Asia [111, 112].

5. Conclusion

A rising trend of reporting histoplasmosis was observed in many areas in Asian countries. Diabetes becomes a notable risk factor among HIV-negative patients with histoplasmosis in Asia. However, the actual number of cases is still far underdiagnosed because of the lack of awareness of the clinician, minimum laboratory facilities to diagnose and the unspecific appearance of histoplasmosis often mimicking other endemic disease in Asia such as tuberculosis. Most of the studies in Southeast Asia were from a case study; a cohort study with a large number of patients is needed to reveal the clinical characteristic and evaluate the management of histoplasmosis in this region. There are an increased number of immunocompetent cases of histoplasmosis from India and China indicating that *Histoplasma* is capable to cause a disease both in immunocompromised and immunocompetent patients. There is an urgent need of proper epidemiology study of histoplasmosis to draw the actual map of histoplasmosis in Asia in order to increase the awareness of clinicians and also to facilitate early diagnosis and management of patients.

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