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Histoplasmosis in southeast Asia and Indian subcontinent: An update

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ABSTRACT

Histoplasmosis caused by *Histoplasma capsulatum* var. *capsulatum* occurs worldwide being predominant in North America and Central America. Southeast Asia (SEA) and Indian subcontinent are areas of low endemicity with rates of prevalence varying in different countries. This review aims at providing an update on different aspects of histoplasmosis in SEA and the Indian subcontinent. A thorough search of the literature on histoplasmosis in SEA and the Indian subcontinent was made in PubMed, MEDLINE, Biomed Lib, Med Facts, using different keywords. Cross references in the relevant articles were used to down load the papers and extract important and pertinent information for incorporation int the review. The updated data on prevalence of histoplasmosis, sensitivity to the antigen histoplasmin and natural occurrence of *H. capsulatum* in different countries in southeast Asia and the Indian subcontinent is described. The varying clinical and pathological features of the cases are reviewed. The need for carrying out comprehensive studies to estimate the actual burden of histoplamosis in in (SEA) Asia and the Indian subcontinent is emphasized. A suggestion is made to augment the laboratory facilities and train laboratory personnel in the latest methods including molecular techniques to achieve this objective.

Keywords: Histoplasmosis, Prevalence, *Histoplasma capsulatum*, Sensitivity, Soil, Clinical features

INTRODUCTION

Histoplasmosis, a systemic mycosis is caused by a dimorphic fungus, *H. capsulatum* var. *capsulatum*; it is often referred to as classical histoplasmosis, or American histoplamosis. Histoplasmosis has a worldwide distribution being predominant in North America and Central America. Southeast Asia (SEA) and Indian subcontinent are areas of low endemicity with rates of prevalence varying in different countries. (Kaufman, 2007). Infection is acquired by inhalation of microconidia/hyphal fragments of *H. capsulatum* from environmental sources (soil/old dried avian or bat excreta). Following inhalation, the fungal elements are engulfed in the pulmonary macrophages, wherein they convert to yeast form of the fungus, multiply and traverse to hilar and mediastinal lymph nodes (Kaufman, 2007; Wheat *et al.,* 2016) The yeast form of the fungus then gets access to the blood circulation system, and disseminates more rapidly and swiftly across various organs of the body. About after two weeks of exposure, the macrophages become fully fungicidal, and the cellular immunity starts a defense against the fungal particles (Wheat *et al.,* 2016). It leads to necrosis at the sites of infection in lungs, liver, spleen, lymph nodes, bone marrow, adrenal glands, and mucocutaneous membranes, which results in progressive disseminated histoplasmosis (PDH). PDH is much more lethal and severe as compared to other kinds of histoplasmosis (Wheat *et al.,* 2016). The present study aims to give an update on histoplasmosis in Southeast Asia (SEA) and the Indian subcontinent.

SEARCH CRITERIA

A thorough search of the literature on histoplasmosis in SEA and the Indian subcontinent was made in PubMed, MEDLINE, Biomed Lib, Med Facts, using sets of different keywords, *viz.* India, Bangladesh, Pakistan, Nepal, Sri Lanka, Bhutan, histoplasmosis, systemic/deep mycoses, etc. The Boolean operator 'AND' was used to combine and narrow the searches. Cross references in the relevant articles were used to down load the papers and extract important and pertinent information for incorporation int the review. Additional information was obtained by searching the medical libraries for journals not listed in the data base.

RESULTS

Prevalence of histoplasmosis

From China, 300 cases were reported between 1990-2011, 75% of them occurring along the Yangtze River. Most of the cases are autochthonous; 43 patients had pulmonary histoplasmosis and 257 had disseminated histoplasmosis; the common underlying diseases included HIV infection, diabetes mellitus and liver diseases (Pan *et al.,* 2013). The number of cases reported from other Southeast Asian countries was Thailand- 233, Malaysia-76, Indonesia- 48, and Singapore-21, only few or no cases reported in other countries (Pan *et al.,* 2013). A survey of medical records of Khon Kaen University affiliated Srinagarind Hospital, Thailand providing healthcare to a population of nearly 1,500,000 inhabitants revealed 34 cases of histoplamsosis during the periods 1996-2002 (Mootsikapun *et al.,* 2006) of these (90.6%) were in AIDS patients. An earlier review in 1960 mentioned one case each from Laos and Myanmar (Randhawa, 1970). The number of cases reported from south Vietnam was 9 (Hoang *et al.,* 2017). In the Indian subcontinent, 426 cases were reported from different parts of India up to 2018, largest number being from West Bengal, followed by Uttar Pradesh, Delhi, Rajasthan, and Maharashtra as mentioned in a review by Randhawa and Gugnani (2018). Subsequently two cases have been reported form Delhi (Butta *et al.,* 2019; Agarwal *et al.,* 2020), three from Rajasthan (Samadhar *et al.,* 2013; Yadav *et al.,* 2021) and one each from Uttar Pradesh (Pandey *et al.,* 2019), Assam (Hawaibum *et al.,* 2021), West Bengal (Sen *et al.,* 2020), and Pondicherry (Roy *et al.,* 2021). Thus, the total number of cases of histoplasmosis reported so far from India is 435. The number of cases from other countries in the Indian subcontinent was Bangladesh-20, Nepal-5, Pakistan-4, and Sri Lanka-3 (Randhawa and Gugnani, 2018). With the reports of eight additional cases from Bangladesh (Chowdhary *et al.,* 2019; Nahar *et al.,* 2020; Rahim *et al.,* 2020) and one from Sri Lanka (Jayathilake *et al.,* 2021), the number of cases of histoplasmois in these countries stands at 28 and 5 respectively. Jahan *et al.* (2021) described 28 cases of adrenal

Fig. 1: Distribution of cases of histoplasmosis in SEA and in the Indian subcontinent



histoplasmosis from Bangladesh, Nepal, and Maldives, but the country-wise distribution of the cases could not be known. The clinical spectrum of the cases in SEA and Indian subcontinent varied from mild influenza-like illness to acute pulmonary histoplasmosis with non-productive cough, chest pain, dyspnea, fever, myalgia, weight loss, malaise and fatigue as described in the aforesaid publications. Progressive disseminated histoplasmosis was mainly characterized by hepatosplenomegaly, generalized lymphadenopathy, anemia, weight loss, pulmonary symptoms being less prominent. Some unusual clinical features in the recently reported cases included intrathoracic mass (Pandey *et al.,* 2019) bilateral endogenous endopthalmitis in disseminated histoplasmosis secondary to immunosuppression (Hawaibum *et al.,* 2021), oropharyngeal mass lesions (Chowdhary *et al.,* 2019: Roy *et al.,* 2021) and chronic liver disease with portal hypertension (Nahar *et al.,* 2020).

The geographic distribution of cases in SEA and Indian subcontinents is depicted in the figure 1. This figure excludes mention of one case each from Laos and Myanmar.

Histoplasmin skin sensitivity

Histoplasmin skin test positivity in China ranged from 6% to 50% in the different population groups., *viz.* 157 students aged 17-22 years, 114 healthy workers aged 17 to 38 years, and 28 hospitalized patients of active tuberculosis aged 17 to 70 years (Wen *et al.,* 1996). In India. a survey of skin testing with histoplasmin on small segments of population residing in rural, urban and riverine area of Delhi during the period recorded a prevalence of 12.3% histoplasmin reactivity in the riverine area, the highest reported from any part of India; however, no case of histoplasmosis was detected among the positive reactors (Vishwanathan *et al.,* 1960). Subsequently several surveys by other investigators showed varying levels of histoplasmin sensitivity up to 10%) (Randhawa and Khan, 1994). Skin testing surveys of histoplasmin sensitivity in Bangladesh, (erstwhile East Pakistan) (Islam *et al.,* 1962; Islam *et al.,* 1971) reported positive skin reactions in 12-23% in the different population groups tested. The staff and students of an agricultural farm area including dairy and poultry farms had significantly higher rates of skin reactivity to histoplasmin than nurses, students, workers in a jute mill, and workers in a paper mill; 23.2% of the reactors had pulmonary calcifications, consistent with resolved acute histoplasmosis (Islam *et al.,* 1971). Histoplasmin sensitivity survey in Sri Lanka carried out in June and July 1969 included 1366 persons comprising students and prisoners, of whom 842 were females and 524 males (Uragoda *et al.,* 1971). All the subjects were over 18 years of age and came from different parts of the country. There were only 78 persons (5.7%) with reactions of 8 mm or over. Only 4 persons (0.3%) had reactions of 8 mm or more (Uragoda *et al.,* 1971). The

reactions to histoplasmin were much stronger in the 133 tuberculosis patients, in contradiction to the rest of the findings, radiological evidence of calcification was seen in 17 (1.2%) of the 1 366 subjects: 15 persons showed it in the hilar region. The histoplasmin reactions in the group with calcifications ranged from 0 to 9 mm with an average of 2.7 mm (Uragoda *et al.,* 1971). In the Punjab region of Pakistan on histoplasmin testing 575 subjects, comprising healthy men, women, and school children as well as pulmonary tuberculosis and leprosy patients in different areas of the Punjab region of Pakistan, all were found to be non-reactors, except who presumably been exposed to the fungus in some other country (Siddiqi and Stauffer, 1980). The authors of this article stated that histoplasmosis is not endemic in this area; however, this conclusion is erroneous since four cases of histoplamosis have been reported from Pakistan (Randhawa and Gugnani, 2018).

Occurrence of *H. capsulatum* in soil

There is only scanty information on occurrence of *H. capsulatum* from soil or other environmental sources in the region of SEA and Indian subcontinent; hence the ecologic niche for this infection remains unclear (Chakrabarti and Salvin, 2011). The country in Asia where *H. capsulatum* was first recovered from soil samples (from a bat infested cave) is Malaysia. (Poonamplan, 1963). *H. capsulatum* was also detected in soil in Thailand from 7 of 77 samples contaminated with bat guano, one of 21 samples contaminated with pigeon droppings, and 10 of 91 samples admixed with chicken droppings by employing Nested PCR (Norkaew *et al.,* 2013). In the Indian subcontinent, there is only one report of its isolation from a sample of soil admixed with guano of the bat, *Sitophilus heathi* in Serampur, near Kolkata, situated on the Ganges river bank (Sanyal and Thammayya, 1975). All of the 209 soil samples collected from other areas in and around Kolkata were negative for *Histoplasma* (Sanyal and Thammayya, 1975).

DISCUSSION

This review gives an update of the current status of histoplasmosis in in Southeast Asia (SEA) and Indian subcontinent. It is possible that many more cases of histoplasmosis than that known so far occur in Pakistan, Nepal and Sri Lanka in the Indian subcontinent, and also in some SE Asian countries, namely Vietnam and Myanmar but have not been detected. There is also need to investigate possible occurrence of histoplasmosis in Cambodia (in SE Asia) and in Bhutan (in Indian subcontinent) from where no case has been reported so far. Histoplasmosis poses a difficult diagnostic challenge because of its highly protean clinical manifestations. Presence of ***military*** shadows in chest X-ray is frequently attributed to tuberculosis without further etiological investigation. Pulmonary histoplasmosis is often misdiagnosed empirically as tuberculosis. In tuberculosis endemic regions, histoplasmosis must be considered in the differential diagnosis in patients with prolonged fever, hepato-splenomegaly, and lymphadenopathy, muco-cutaneous lesions, inflammatory bowel disease, particularly, if ***AFB*** smear and cultures are negative for *Mycobacterium tuberculosis* and there is no response to empirical ***ATT***. Several media have been employed for isolation of *H. capsulatum* from clinical specimens. Brain heart infusion (BHI) agar biphasic medium, BHI agar and yeast phosphate agar are best for maximizing the recovery of *H. capsulatum* and cultures of clinical specimens should be examined up to 3 weeks (Randhawa and Gugnani, 2018). Serological and molecular techniques should be employed as an additional method. Serological evidence is an important factor in the diagnosis of histoplasmosis. Such evidence may be obtained through a CF and ID antibody test used singly or in combination or by the new RIA for *H. capsulatum* glyco-protein antigen in serum and urine (Wheat *et al.,* 2016). Chemo-luminescence labelled for the detection of specific sequences of ribosomal RNA (rRNA) has been employed to detect DNA probe and confirm *H. capsualtum* isolates from the cultures of clinical samples (Azhar and Hage, 2017).

CONCLUSION

The relatively greater paucity of reports of histoplasmosis from Pakistan and Nepal than Bangladesh may be due to lack of awareness, adequate laboratory facilities and trained laboratory personnel. Latest reports of cases of histoplamsosis from India, Bangladesh, and Sri Lanka though few in number indicate a rising trend of the disease in the Indian subcontinent. However, the number of cases of histoplasmosis reported so far from SEA Asia and the Indian subcontinent is only a tip of the iceberg of burden of histoplasmosis. There is need for collaborative comprehensive mycological and epidemiological investigations to estimate the burden of histoplamosis and to map out the endemic areas of the disease in Asia. Laboratory facilities should also be augmented for early and correct diagnosis of histoplasmosis, and for timely therapy of the disease. Efforts should also be made for detecting addition natural foci of *H. capsualatum* tum, in soil, avian and bat habitats by employing mycological and molecular methods.

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