Occurrence of Histoplasmosis in the Indian Sub-Continent: An Overview and Update

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ABSTRACT

The occurrence of histoplasmosis and its environmental sources of infection are reviewed. It covers the regional distribution of 388 cases of histoplasmosis reported since 1995 to till date. The highest number of cases occurred in West Bengal, followed by Uttar Pradesh, Delhi Union territory (UT), Rajasthan, Maharashtra, Haryana, and Bihar. A sharp rising trend in reporting cases observed in recent years is particularly noteworthy. Also, discussed are the variable clinico-pathological manifestations of 388 cases from India, 20 from Bangladesh, five from Nepal, four from Pakistan, and three from Sri Lanka. Being a primary pathogen, the etiological agent Histoplasma capsulatum can infect immunocompetent as well as the immunocompromised patients. The disease is fatal unless diagnosed early and treated with specific antifungal drugs. It has a predilection for reticuloendothelial system, leading to hepatosplenomegaly, a prominent feature of disseminated histoplasmosis. It poses an ever-increasing threat to public health due to burgeoning population of immunocompromised patients resulting from the spread of AIDS and immunosuppressive therapy in patients undergoing organs transplantation. Non-recognition of the true burden of histoplasmosis in the Indian sub-continent is attributed to possible misdiagnosis as tuberculosis, malignancy or other diseases, and to lack of awareness and inadequate mycological diagnostic facilities. The need for exploring the natural foci of the pathogen and its occurrence in the endemic zones of histoplasmosis is strongly emphasized.

Core tip Nomenclature of Histoplasma, its ecology, pathogenesis, clinical spectrum and laboratory diagnosis, and regional distribution of histoplasmosis in India are described. The highest number of cases of the disease occurred in West Bengal. The varying clinical manifestations of 388 cases from India, 20 from Bangladesh, five from Nepal, four from Pakistan, and three from Sri Lanka are described. The decade-wise occurrence of histoplasmosis in India showed a rising trend of reporting 200 cases being recorded during the period 2004–2013, and 161 cases from 2014 to till date. In view of the available evidence, histoplasmosis is endemic in the subcontinent. However, supportive scientific evidence like demonstration of natural reservoirs of the pathogen and its occurrence in the local animal populations remains largely unexplored.

KEYWORDS histoplasmosis, Histoplasma capsulatum var. capsulatum, Indian, subcontinent, update

INTRODUCTION

Histoplasmosis is a non-contagious systemic fungal infection of worldwide distribution, caused by a thermally dimorphic fungus, Histoplasma capsulatum which thrives in a warm and humid environment such as soils enriched with nitrogenous compounds and phosphates derived from avian excreta and bat guano. The microconidia and short hyphal fragments of Histoplasma when inhaled by mammalian hosts reach the alveoli, followed by the rapid conversion to its yeast form that can persist in host tissues and may disseminate through the bloodstream and lymphatics to other organs, causing histoplasmosis. The organism may also enter the body through the mouth, and from there can cause infection in the intestines1,2. Histoplasmosis in humans has two clinical entities: Histoplasmosis capsulati caused by H. capsulatum var. capsulatum (Darling’s disease, American histoplasmosis, classical histoplasmosis, small form histoplasmosis), and Histoplasmosis duboisi caused by H. capsulatum var. duboisi, commonly called African histoplasmosis (large form histoplasmosis). Investigators linked to the division of medical mycology, VPCI, have been interested since 1960 in clinical and epidemiological aspects of histoplasmosis. The first case of histoplasmosis from India was reported in 1954 by Panja and Sen4 during the period 1957–1959. The prevalence of 12.3% histoplasmin sensitivity found in the riverine area was the highest reported from any part of India. However, no case of histoplasmosis was detected among the positive reactors. Data on histoplasmin sensitivity in other parts of India have been reviewed by Randhawa and...
Khan. Since then, the disease has been the subject of a large number of case reports, and several reviews. A rare case of epidymal histoplasmosis masquerading as tuberculosis diagnosed by semen was reported by Randhawa et al. This paper reviews the clinico-pathological and epidemiological features of the 388 cases of histoplasmosis, reported in India since 1995, and also those reported from Bangladesh, Nepal, Pakistan, and Sri Lanka.

METHODS

All publications on histoplasmosis in the Indian sub-continent were scanned by thorough search of the literature, using PubMed, MEDLINE, Biomed Lib, Med Facts, and different sets of keywords, viz. India, Bangladesh, Pakistan, Nepal, Sri Lanka, Bhutan, histoplasmosis, systemic/deep mycoses, etc. Besides, cross-references in the papers collected were accessed. All of the papers were critically reviewed to extract relevant clinico-pathological features and demographic data of each case. Cases diagnosed solely on clinical suspicion without histopathological evidence or positive cultures were excluded.

OBSERVATIONS

Nomenclature of Histoplasma and its ecology

Histoplasmosis has three clinical entities with separate etiologic agents (Table 1). Based on phenotypic characters, Histoplasma is divided into three varieties, viz. H. capsulatum var. capsulatum, H. capsulatum var. duboisii and H. capsulatum var. farciminosum. The commonest environmental sources of H. capsulatum var. capsulatum are soil around chicken houses, under roosting gregarious birds such as starlings, blackbirds, and soil of bat-infested caves or old buildings (CFU can exceed 10^5/g of soil/bat guano). Birds cannot be infected by the fungus and do not transmit the disease. However, avian excreta contaminate the soil, thereby providing an enriched medium for the fungus. On the other hand, bats can get infected and transmit H. capsulatum to new sites through their droppings. The fungus is found in the upper 15 cm of soil, never deeper than 22.5 cm, and requires a mean temperature of 22–29°C and relative humidity of 67–97% for optimum growth. Activities such as cleaning of chicken coops, visiting bat-infested caves or other such sites, excavation, demolition and remodeling of old buildings, and cutting of dead trees lead to disruption of soil containing the organism, and aerosolization of microconidia.

Clinical spectrum and laboratory diagnosis

Histoplasmosis caused by H. capsulatum var. capsulatum is a disease of reticuloendothelial system. A majority (50–90%) of the infections result in clinically insignificant respiratory disease or mild influenza-like illness. Some infections may cause acute pulmonary histoplasmosis, manifested by non-productive cough, dyspnea, hoarseness, chest pain, cyanosis associated with fever, night sweats, muscle/joint pain, weight loss, malaise, and fatigue. Acute pulmonary histoplasmosis may be confused with tuberculosis/miliary tuberculosis, although involvement of upper lobes and pleural effusion is more common in the latter. Chest X-ray findings in most patients with asymptomatic pulmonary histoplasmosis are normal. A single pulmonary nodule is, however, frequently seen. Most patients recover within 2 weeks of onset of symptoms, although fatigue may persist longer. Progressive disseminated histoplasmosis occurs in approximately 10% of the patients with hepatosplenomegaly, fever, anemia, leukopenia, weight loss, and generalized lymphadenopathy; pulmonary symptoms being less prominent. Males are more frequently affected than females by 4:1 ratio. Patients with AIDS are at high risk for disseminated histoplasmosis; prevalence rates range is 2–27% in United States and 29% in India.

Laboratory diagnosis of histoplasmosis is based on histopathology/cytopathology, recovery of Histoplasma in culture from clinical samples, serological tests for antibodies, and antigen detection. Cultures are 58–85% positive in cases of disseminated and chronic forms of histoplasmosis; usually, up to 4 weeks is required to isolate the organism in culture. Several culture media have been used for recovery of H. capsulatum var. capsulatum from clinical specimens. In our experience, brain-heart infusion (BHI) biphasic medium appears to be the best for recovery of the organism. Antigen detection by latex agglutination assay is a practical and rapid approach for the diagnosis of histoplasmosis.

### Table 1: Nomenclature of Histoplasma, natural habitats and geographic distribution.

<table>
<thead>
<tr>
<th>Etiological agent*</th>
<th>Clinical entity</th>
<th>Yeast form morphology</th>
<th>Natural habitat</th>
<th>Geographic distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. capsulatum var. capsulatum</td>
<td>Histoplasmosis (histoplasmosis capsulati, classical histoplasmosis)</td>
<td>Globose or ovoid 2–4 μm, thin-walled cells with a narrow base</td>
<td>Soil enriched with avian or bat excreta</td>
<td>Worldwide with variable endemcity</td>
</tr>
<tr>
<td>H. capsulatum var. duboisii</td>
<td>Histoplasmosis duboisii (African histoplasmosis)</td>
<td>Ovoid 6–15 μm thick-walled cells with a broad base</td>
<td>Rarely isolated from soil</td>
<td>Central and West Africa, and Madagascar</td>
</tr>
<tr>
<td>H. capsulatum var. farciminosum</td>
<td>Histoplasmosis farciminosi (epizootic lymphagitis)</td>
<td>Ovoid 2–3 μm, thin-walled cells with a narrow base</td>
<td>Unknown</td>
<td>Africa, Asia and Europe</td>
</tr>
</tbody>
</table>

*Studies of isolates of H. capsulatum from Europe, Australasia, Asia, Netherlands, North America and South America by Kasuga et al. and Teixeira et al. have detected several phylogenetic clades, suggesting that the existing varieties are taxonomically invalid.
for rapid recovery of maximum growth of *H. capsulatum*. Yeast phosphate and BHI agar are nearly as good as these media also recover multiple colonies of the fungus. Galactomannan antigen detection in body fluids offers a rapid means of diagnosis. The antigen is detectable in 80–95% of cases of progressive disseminated and subacute histoplasmosis.

**Magnitude of problem in India**

The data on the occurrence of histoplasmosis in India reported since 1995 is presented in Table 2 and depicted in Fig. 1. West Bengal accounted for the highest number of 56 cases, followed by Uttar Pradesh, Delhi (UT), Rajasthan, Maharashtra, Haryana, and Bihar. The diagnosis of a majority of the cases was based on histological/cytopathological demonstration of the characteristic yeast form of *H. capsulatum*. Confirmation by culture was done in about 20% of the cases. Additional tests, viz. serology, PCR, and sequencing were done only in a few cases. The literature search did not reveal the
occurrence of any case from the States of Arunachal Pradesh, Goa, Mizoram, Nagaland, and Sikkim, and the Union Territories of Daman and Diu, Dadra and Nagar Haveli and Pondicherry, and Andaman and Nicobar, and Lakshadweep islands. Histoplasmosis possibly occurs in these areas but has not been detected due to lack of awareness among the physicians and paucity of laboratory diagnostic facilities. It is noteworthy that a large number of cases of oral and adrenal histoplasmosis (mostly in renal transplant recipients) have been documented during the period under review. The decade-wise occurrence of histoplasmosis is shown in Table 3 and depicted in Fig. 2. Notably, the number of cases reported during the period 1954–1993 was 37, followed by a sharp rising trend of reporting. Thus, 200 cases were recorded during the period 2004–2013, and 161 during the period from 2014 to till date. This significant change can be attributed to increased awareness among clinicians, pathologists and microbiologists, and their collaboration. The availability of enhanced laboratory facilities in many medical colleges and hospitals in some parts of the country is another contributing factor for increased reporting from those areas.

The predominant clinical features and the involvement of different organs in the cases reviewed were essentially the same as described previously. The commonest comorbidities were HIV infection, diabetes, adrenal insufficiency, and renal transplant. It is noteworthy that adrenal histoplasmosis was frequently observed in transplant recipients. Adrenal involvement also seems to be common in immunocompetent patients with disseminated histoplasmosis. Sometimes cutaneous lesions were the only sign of serious systemic histoplasmosis in post-transplant patients. A number of cases occurred in association with hemophagocytic lymphocytosis, other unusual comorbidities included hairy cell leukemia with ascites, juvenile SLE, lymphoid co-infection with cryptococcosis, CMV infection, aplastic anemia, Coomb's positive hemolytic anemia, myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN), mixed phenotype leukemia, and BK virus nephropathy. Another unusual case of comorbidity was the occurrence of rectal histoplasmosis in a patient with Job's syndrome. A few cases of oral histoplasmosis simulated carcinoma, whereas some laryngeal/pulmonary/disseminated cases mimicked lung and laryngeal carcinoma. Likewise, one case simulated lepromatous leprosy, non-Hodgkin lymphoma, idiopathic thrombocytopenic purpura, abdominal tuberculosis, Langerhans cell histiocytosis, and two cases of eyelid involvement simulated basal cell carcinoma. Some other unusual presentations of histoplasmosis were parenchymal diseases with ascites, colonic pseudotumors, portal hypertension with bone involvement, pancreatic head mass with gastric outlet obstruction, and epididymitis and prostatitis. The frequent involvement of gastrointestinal tract in several cases as observed in the current review points out the need for considering gastrointestinal histoplasmosis in the differential diagnosis of malignancy, inflammatory bowel disease, and intestinal tuberculosis. Oral lesions were common in the series of cases in our review, involving several sites, viz. buccal mucosa, tongue, gingivae, and palate; in many of the cases there was no indication of pulmonary lesions. However, the prior occurrence of self-resolving pulmonary histoplasmosis cannot be ruled out. In tuberculosis-endemic regions as in the Indian sub-continent, disseminated histoplasmosis can easily be mistaken for tuberculosis owing to its similar clinical presentation. Presence of military shadows in chest X-ray is frequently attributed to tuberculosis without further etiological investigation. In patients with prolonged fever, hepatosplenomegaly, and lymphadenopathy, histoplasmosis must be considered in the differential diagnosis, particularly, if there is no response to empirical anti-tubercular therapy (ATT). Further, in patients of pulmonary histoplasmosis with pre-existing lung disease, hilar, and peripheral lymphadenopathy, radiological signs suggestive of histoplasmosis may not be present. Also, several cases of histoplasmosis in the subcontinent may present as non-healing oral ulcers mimicking mucocutaneous leishmaniasis. It needs to be emphasized that histoplasmosis should be considered in the differential diagnosis of patients with mucocutaneous lesions,

<table>
<thead>
<tr>
<th>Period</th>
<th>No. of cases</th>
</tr>
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<tbody>
<tr>
<td>1954–1963</td>
<td>4</td>
</tr>
<tr>
<td>1964–1973</td>
<td>14</td>
</tr>
<tr>
<td>1974–1983</td>
<td>12</td>
</tr>
<tr>
<td>1984–1993</td>
<td>7</td>
</tr>
<tr>
<td>1994–2003</td>
<td>28</td>
</tr>
<tr>
<td>2004–2013</td>
<td>200</td>
</tr>
<tr>
<td>2014-to-date</td>
<td>161</td>
</tr>
<tr>
<td>Total</td>
<td>426</td>
</tr>
</tbody>
</table>

Fig. 2 Data on decade-wise occurrence of histoplasmosis in India, showing a sharp rising trend in its reporting during the decade 2004–2013, and thereafter during the period of 2014-to-date.
hepatosplenomegaly, adrenal insufficiency, malignancy, inflammatory bowel disease, and in patients clinically diagnosed as oral and abdominal tuberculosis.

**CASES IN BANGLADESH, NEPAL, PAKISTAN, AND SRI LANKA**

A brief account of the histoplasmosis cases reported from Bangladesh, Nepal, Pakistan, and Sri Lanka is given in Table 4 along with references.

**Bangladesh**

In a histoplasmin skin sensitivity survey in Bangladesh (when it was called East Pakistan) in 1962, 2,729 persons, including patients in the hospital, students and nurses, workers in a jute mill, a paper mill, and staff and students of an agricultural farm area were tested. There was no significant difference in the number of positive reactors to histoplasmin in the first four groups (12.58–13.75%), but the number of positive reactors in the agricultural farm was nearly double (23.18%) of that of any other group. Subsequently in 1971, 461 of 2,522 (17.92%) patients in institutions of tuberculosis and other chest diseases were found to be positive reactors. These surveys indicated endemicity of histoplasmosis in Bangladesh. Recently, an increasing number of histoplasmosis cases have been reported. The clinico-epidemiological features of 20 published cases are provided in Table 4. All of the patients were adult males of aged 30–75 years. As is evident, most of the cases were disseminated with varying clinico-pathological manifestations, viz. hepatosplennomegaly, generalized lymphadenopathy with oropharyngeal and laryngeal ulcers, bilateral adenomegaly, and skin lesions in the form of a generalized maculopapular rash or hyperpigmented skin nodules. Four of the patients had AIDS, one of them with concurrent esophageal candidiasis; in addition to the five patients gave a history of TB with ATT. One of the patients had Crohn’s colitis. It is worth mentioning that eight of the patients were farmers, and one each was a building maintenance and brickfield worker. One of the patients, immigrant in New York (Sr no 5) had made several visits to Bangladesh, the last one 6 months prior to his illness. Diagnosis of all the cases was based on histopathology, barring one culture positive for *H. capsulatum*.

**Nepal**

Four autochthonous cases have been reported. Additionally, one case has occurred in a Nepalese migrant to United States with evidence of infection being acquired in Nepal (Table 4). Four of these cases

<table>
<thead>
<tr>
<th>Sr. no</th>
<th>Age/sex</th>
<th>Place of reporting</th>
<th>Clinico-pathological manifestations</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladesh</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>45 M</td>
<td>Dhaka</td>
<td>Generalized lymphadenopathy, oral ulcers, odynophagia fever, ascites, weight loss</td>
<td>Shamin Ahmad Md et al. BSMMU J. 2010;3:44–46</td>
</tr>
</tbody>
</table>
TABLE 4  Histoplasmosis in Bangladesh, Nepal Pakistan, and Sri Lanka—(Continued).

<table>
<thead>
<tr>
<th>Sr. no</th>
<th>Age/sex</th>
<th>Place of reporting</th>
<th>Clinico-pathological manifestations</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>30 M</td>
<td>Northern Bangladesh (Place unspecified)</td>
<td>Cough, fever, weight loss, anorexia, hyper-pigmented papular eruptions on several parts of the body, bleeding from ear, nose, gums and rectum, severe anemia with AIDS</td>
<td>Bhuyian MNZ et al. JAFMC Bangladesh. 2012;8(2):81–86.</td>
</tr>
</tbody>
</table>

**Nepal**


**Pakistan**

| 4      | 60 M    | Battagram         | Chest pain, weight loss, dry cough, pleural effusion with h/o of ATT and left hydro-pneumothorax and long standing diabetes | Aziz R et al. Unpublished data from Ayub Teaching Hospital, Abbottabad. |

**Sri Lanka**

were disseminated, involving the lung, liver and spleen, or adrenal glands; the fifth had multiple discharging lesions on the anterior chest wall for the last 6 years. Four of the patients were males and one female. One of the males, a 14-year-old boy was persistently exposed to chickens, and had a history of rheumatic heart disease, complicated by severe mitral stenosis. Two of the patients were farmers, one of whom (Sr. no 4) had recently migrated to New York, United States.

Pakistan

Altogether 575 subjects, comprising healthy men, women, and school children, as also pulmonary tuberculosis and leprosy patients in Punjab province of Pakistan, were tested for skin sensitivity to histoplasmin. All of the subjects were non-reactors, excepting those who had traveled abroad to endemic areas indicating non-endemicity of histoplasmosis in Pakistan. Our literature search has now revealed four authentic indigenous cases of histoplasmosis (Table 4). Three of them had symptoms of disseminated histoplasmosis with prior history of ATT; the fourth was an unusual case of Histoplasma endocarditis.

Sri Lanka

A survey of histoplasmin sensitivity conducted in 1969 comprised of 1,366 students and prisoners (524 males, 842 females). This included 133 tuberculosis patients diagnosed by bacteriologic or histopathologic examination from different parts of the country. Notably, this group revealed 78 strongly positive reactors. However, only three autochthonous cases of histoplasmosis have been documented so far. One of them, a 24-year-old German woman had possibly acquired infection in Sri Lanka or Maldives, while on a 10 days holiday trip to this region.

Information on the occurrence of African histoplasmosis in the Indian subcontinent is lacking. The case reported by Ravindran et al. in 2015 from Kerala state of India lacks authentication. The photomicrograph provided in Fig. 6 of this publication is entirely incompatible with H. capsulatum var. duboisii. It depicts arthroconidia like bodies suggestive of Trichosporon and not the large yeast form cells characteristic of H. capsulatum var. duboisii.

HISTOPLASMOSIS IN ANIMALS

Histoplasmosis has been reported in several species of small mammals including wild rats and opossums. Demonstration of histoplasmosis in animals helps to establish endemicity of the disease in a given area. There is no report of isolation of Histoplasma from small mammals in India. Kalra and Wanchoo reported negative findings in investigation of 325 rats, 65 bandicoots, nine shrews, and four house mice examined from Pune State of Maharashtra. Investigation of 630 small wild animals belonging to 11 species and 10 genera from different parts of India by Gugnani did not yield any isolation of this fungus. Epizootic lymphangitis caused by H. capsulatum var. farciminosum has been reported in equines and camels from several countries including India.

SOIL AS NATURAL HABITAT OF H. CAPSULATUM VAR. CAPSULATUM

Information on the natural habitats of H. capsulatum var. capsulatum in the Indian subcontinent is restricted to a single report of its isolation from a sample of soil admixed with bat guano. The sample was collected from a 300-year-old building infested with bats of the species Scotophilus heathi in Serampur, near Kolkata, situated on the Ganges river bank. All of the 209 soil samples collected from other areas in and around Kolkata were negative for Histoplasma. Likewise, 523 soil samples collected from chicken pens, bat-infested sites, and rat burrows in India and Nepal were negative. Besides, 236 samples of avian excreta examined from Delhi and other parts of India and 419 samples of bat guano/soil and avian excreta examined from Delhi were also negative. Randhawa et al. (unpublished data). Considering that many of the cases in our review gave history of exposure to bats in old buildings, the need for further environmental studies, using molecular techniques, can hardly be overemphasized.

CONCLUDING REMARKS

Histoplasmosis poses a difficult diagnostic challenge because of its highly protean clinical manifestations. Being a primary pathogen, the etiologic agent, H. capsulatum var capsulatum infects the immunocompetent as well as immunocompromised patients. At room temperature (25–30°C) in the laboratory, H. capsulatum var. capsulatum appears as a slow growing mold, requiring 3–6 weeks for its cultivation. Although culture has been considered as the gold standard among the laboratory diagnostic tests, its value is limited by the fact that most of the diagnostic microbiology laboratories in the hospitals discard their cultures after 48–72 hours. Moreover, Sabouraud agar routinely used as a mycological medium is unsuitable for this fastidious fungal pathogen. To add further to these difficulties, direct microscopy of wet mounts or stained tissue sections/smears of clinical specimens is lacking in sensitivity and requires expertise of a cytopathologist/histopathologist for interpretation. The afore-mentioned difficulties have been overcome with the development of PCR but this molecular technology is not accessible to a vast majority of the diagnostic centers in the Indian subcontinent. Further studies applying the latest molecular techniques are strongly indicated. Disseminated histoplasmosis is fatal unless diagnosed early and treated with specific antifungal
agents. *Histoplasma capsulatum* var. *capsulatum* has a predilection for the reticuloendothelial system. Hence, hepatosplenomegaly is a prominent feature of disseminated histoplasmosis.

A sharp rising trend in the number of histoplasmosis cases reported in recent years is a notable observation. This is attributable to increased awareness apart from further development and expansion of mycological diagnostic facilities. Although its occurrence is widespread, the burden of disease in the subcontinent remains underdetermined due to paucity of systematic and comprehensive studies, using recently introduced molecular techniques. Considering that an overwhelming number of the cases had not traveled abroad to the endemic areas of the disease in North America, the disease is endemic in the subcontinent. However, supportive scientific evidence like the demonstration of natural reservoirs of the pathogen and its occurrence in the local animal populations remains largely unexplored. To sum up, our current knowledge of the global geographic distribution of his- 

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to the distribution of mycologists more accurately than it does the distribution of mycoses and their relative importance in a given area.

**ACKNOWLEDGMENT**

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**REFERENCES**


Histoplasmosis in the Indian subcontinent
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