A Twenty-First-Century Perspective of Disseminated Histoplasmosis in India: Literature Review and Retrospective Analysis of Published and Unpublished Cases at a Tertiary Care Hospital in North India

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Abstract
Purpose Published literature lacks systematic studies on disseminated histoplasmosis in India, and previous reviews on its epidemiology in India were conducted two decades back. Thus, we review the Indian studies published in this century to understand the recent epidemiology of histoplasmosis in India and do a retrospective analysis of all cases diagnosed at our institute.

Methods A literature of review search was done in Pubmed/Medline and Scopus. Studies published during January 2001–December 2015 were considered along with retrospective analysis of cases presented to us. A distinction was made in the clinical presentation of immunocompetent and immunocompromised cases.

Results Ninety-five included studies described 204 cases, and 10 cases from our retrospective analysis were included. The mean age at presentation was 45.1 ± 15.4 years [range 3–83, median 45, interquartile range 37–55], and male-to-female ratio was 6:1. Most cases were reported from northern and north-eastern states of India along the rivers Ganges, Yamuna and Brahmaputra and in people associated with agricultural activity. About 33% of cases were immunocompromised, out of which immunosuppression due to HIV was seen in 72% cases. The mean age of presentation was significantly lower in immunocompromised cases (37.9 vs. 49.2 years; \( p < 0.00001 \), Mann–Whitney test), and mortality was also higher (10 vs. 27.5%, \( p = 0.01 \), Fisher’s exact test). Adrenal involvement was in significantly higher proportion of immunocompetent patients compared to immunocompromised population.

Conclusions Disseminated histoplasmosis is being increasingly recognized in India. There is a need to undertake well-designed, analytical studies utilizing appropriate diagnostic modalities to understand the epidemiology of this neglected disease in proper perspective.

Keywords Histoplasmosis · Systematic · Developing · Epidemiology · Review

Background
The dimorphic fungus *Histoplasma capsulatum* is a soil-based fungus, which thrives at environmental conditions typically found in temperate zone between latitudes 45°N to 30°S. It is associated with decaying bird and bat guano and typically found within 20 cm of the surface of the soil which is acidic, moist and
high in nitrogen content. Excavation, construction or recreational activities lead to disruption of soil surface and release of infectious conidia, which are subsequently inhaled. After being engulfed by lung neutrophils and macrophages, mycelia convert to yeast phase and migrate via draining lymphatics predominantly to organs with mononuclear phagocytes. Restriction of intracellular multiplication of yeast occurs via activation of cell-mediated immunity [1].

Of the various clinical presentations of histoplasmosis, disseminated infections occur primarily in immunocompromised subjects, especially in patients with defect in cellular immunity such as HIV with low CD4+ lymphocyte count, patients undergoing cytotoxic chemotherapy, corticosteroid or other forms of immunosuppressive therapy [2, 3]. With continuing advances in medical science, survival of HIV and other immunodeficient patients has improved, which has prolonged their period of immunosuppression, thereby predisposing them for various infections by opportunistic pathogens including *H. capsulatum* [4]. In addition, over the past decade cases of disseminated histoplasmosis have been increasingly reported worldwide in immunocompetent patients particularly in those exposed to a heavy inoculum [2]. Disseminated histoplasmosis can involve multiple organs, and the clinical spectrum can range from non-specific symptoms like mild fever, anorexia, weight loss, cough to hepatosplenomegaly, lymphadenopathy, mucocutaneous lesions and gastrointestinal involvement [1, 2]. Keeping a high clinical suspicion regarding a differential diagnosis of histoplasmosis is required to prevent misdiagnosis particularly in high-risk patients and initiate early antifungal therapy. This necessitates reporting of cases with disseminated histoplasmosis so as to create awareness among clinicians regarding this disease.

Since the first case reported in 1954 [5], a steady increase in occurrence of histoplasmosis is noted in India. Initially, the disease was considered sporadic [6]. However, reviews [7, 8] published in the previous century have shown it to be widespread throughout the country, with area of high prevalence along the Gangetic plains. Systematic studies on histoplasmosis are lacking from India and largely, the information is available from case reports or case series published in the literature. Except for one recent review, [9] done on cases reported from 1995 to 2011 in immunocompetent adults, no study has reviewed the epidemiology of disseminated histoplasmosis in India in this century. In this current publication, we review the status of disseminated histoplasmosis in India through analysis of all studies published in this century. We also present all cases of disseminated histoplasmosis that were diagnosed and treated at our institute in the twenty-first century (till 2015) including new cases that had not yet been published in the literature.

**Methods**

Search strategy: A strategic, literature review search was done in Pubmed/Medline and Scopus using the following MeSH terms: (*Histoplasma capsulatum*), (Histoplasmosis), (Histoplasma, disseminated) and (India). Combinations like (*Histoplasma capsulatum* in India), (*Histoplasma capsulatum* and India), (Histoplasmosis in India), (Histoplasmosis and India), (Histoplasma, disseminated and India) and (Histoplasma, disseminated in India) were used to retrieve the articles. Articles in English published during January 2001 to December 2015 were considered for reviewing. Reference lists of retrieved articles were checked to detect additional articles missed by search strategy.

Inclusion and Exclusion Criteria: Cases were included in accordance with criteria for endemic mycoses by European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and National Institute of Allergy and Infectious Diseases Mycoses Study Group [10]. We defined disseminated histoplasmosis as the presence of intracellular yeast cells suggestive of histoplasma detected by histopathology or cytopathology or direct microscopy or culture of one or more extrapulmonary specimens obtained by needle aspiration or biopsy.

Reports which described cases presented before year 2000 were excluded, but case series which included patients before the year 2000, but without exact year of presentation of individual cases, were included in the analysis. Cases published in peer reviewed journals under sections “photo-letters” and “images” were included, and in the event of duplication, study published earlier was included. The retrieved studies were independently assessed by authors AG1 and AG2. Any disagreement on inclusion of article in the study was resolved by discussion with IX and GS.
In addition to the published articles of cases diagnosed and/or treated in our institute between January 2001 to December 2015, unpublished reports of disseminated histoplasmosis from our institute during this time period were also reviewed retrospectively, analyzed and included. Our institute is an academic, tertiary care institute funded by central government of India. It is located in the capital city of India and caters to patients belonging to the northern states of India, namely New Delhi, UP, Bihar, Haryana, Punjab; and central states, namely Rajasthan and Madhya Pradesh. It is about 1800-bedded, referral center for many diseases and runs specialized diagnostic as well as research laboratories in Mycology.

Data analysis: For each case, data were noted for demographic characteristics, geographical location, travel history, occupational history, clinical presentation, underlying disease, diagnostic modality, treatment given and outcome. Cases where an underlying disease or predisposing factor was mentioned were considered as “Immunocompromised” and where no such predisposing condition and negative HIV serology was mentioned were considered as “Immunocompetent.” Data were managed in Microsoft Excel® and analyzed by Stata, version 7.0 (Stata Corp., Texas, USA). Statistical significance was defined at \( p < 0.05 \).

Results

Identified Studies and Cases

Our search strategy yielded 118 studies (list of all studies in supplemental file), of which 23 were excluded [11–31]. The process of selection and reasons for exclusion are described in Fig. 1. The 95 included studies described 204 cases, and 10 cases from our retrospective review were analyzed (Table 1). Two case series which had reviewed patients presented during periods 1999–2002 [32] and 1998–2009 [33] were included. The number of studies published each year since 2002 is given in Fig. 2. Eighteen studies were reported during 2014 and 2015 [34–50].

New cases at our institute (unpublished data): Clinical and diagnostic details of ten new cases of disseminated histoplasmosis diagnosed and treated at the institute have been summarized in Table 1 (Case no. 11-20). Briefly, out of these 10 patients, the male/female ratio was 4:1. One belonged to pediatric age group (age 11 years), and the mean age of the adults was 48.6 ± 8.6 years (range 40–65 years). The most common presenting signs and symptoms were fever, mucocutaneous ulceration followed by hepatosplenomegaly. The duration of onset of symptoms and diagnosis ranged from 2 to 24 months with a mean of 5 months approximately. Four of these patients were immunocompetent, and three were found to be reactive for HIV. We could do histoplasma M-gene PCR using primers MSP2F and 2R in 2 patients (Case nos. 18 and 20) which provided positive results before culture [51]. However, both of these cases were started on amphotericin B therapy based on histopathology report. A total of 4 patients showed clinical improvement on follow-up.

Demographic Characteristics of All Cases

Age: The mean age at presentation was 45.1 ± 15.4 years (range 3–83, median 45, data available for 152/214). The percentage of cases in each class interval for age is shown in Fig. 3. The mean age at presentation in immunocompromised cases was 37.9 ± 14.0 years (range 4–70, median 40, data available for 53/65) and was significantly lower \(( p < 0.0001 \), Mann–Whitney test) than immunocompetent cases in whom mean age at presentation was 49.2 ± 14.9 years(range 3–83, median 50, data available for 83/119).

Gender: Of 214 cases, information regarding gender was available in 175 cases (data not available for 37 cases in Ref. [46] and 2 cases in Ref. [42]) out of which 150 (86%) were males and 25 (14%) were females. Male-to-female ratio (M:F) was 6:1. The mean age of presentation among female patients was 35.0 ± 15.8 years (range 4–60, median 39, data available for 24/25) and was significantly lower \(( p = 0.001 \), Mann–Whitney test) than male patients in whom mean age was 47.1 ± 14.5 years (range 3–83, median 48, data available for 119/150). Of 53 immunocompromised cases, in whom gender was known, 43 (81%) were males and 10 (19%) were females, whereas of 83 immunocompetent cases, 70 (84%) were male and 13 (16%) were females with no gender predisposition between them \(( p = 0.64 \), Fisher’s exact test; Table 2).

Occupational history: Documentation of occupational history and history of exposure to birds or pets
Fig. 1 Flowchart demonstrating studies which processed for inclusion in our analysis
<table>
<thead>
<tr>
<th>S. No.</th>
<th>Ref.</th>
<th>Yr. of publ./Pres.</th>
<th>Age/sex</th>
<th>State</th>
<th>IC/ID (cond.)</th>
<th>Clinical features</th>
<th>Clinical sample</th>
<th>Histopathology/culture</th>
<th>Treatment/outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>[22]</td>
<td>2005/nk</td>
<td>45/M</td>
<td>nk</td>
<td>IC</td>
<td>Fever, weight loss, papule over face, neck trunk, bilateral adrenal abscesses, adrenal insufficiency</td>
<td>Skin biopsy, adrenal fna</td>
<td>Positive/not done</td>
<td>amB-ic* followed by open drainage/improvement after open drainage of adrenals</td>
</tr>
<tr>
<td>2.</td>
<td>[23]</td>
<td>2010/2007</td>
<td>3/M</td>
<td>nk</td>
<td>IC</td>
<td>Papules over face, trunk, all extremities, groin, buccal and palatal mucosa</td>
<td>Skin biopsy</td>
<td>Positive/positive</td>
<td>amB-ic then vor/relapse after amB-ic cured after vor</td>
</tr>
<tr>
<td>3.</td>
<td>[24]</td>
<td>2008/nk</td>
<td>22/M</td>
<td>New Delhi</td>
<td>ID (renal transplant)</td>
<td>Subcutaneous nodules over trunk and right thigh, past history of disseminated histoplasmosis diagnosed on bone marrow biopsy</td>
<td>Skin biopsy</td>
<td>Positive/positive</td>
<td>amB-ic/improvement</td>
</tr>
<tr>
<td>4.</td>
<td>[76]</td>
<td>2010/2010</td>
<td>39/M</td>
<td>nk</td>
<td>ID (CD4 T-cell lymphocytopenia)</td>
<td>Fever, cough, red nodules on face, neck and legs</td>
<td>Skin biopsy</td>
<td>Positive/not done</td>
<td>ic/improvement</td>
</tr>
<tr>
<td>5.</td>
<td>[77]</td>
<td>2010/nk</td>
<td>62/M</td>
<td>nk</td>
<td>IC</td>
<td>Dysphagia, loss of weight, pharyngeal mass, bilateral adrenal enlargement</td>
<td>Laryngeal biopsy</td>
<td>Positive/not done</td>
<td>amB-ic/improvement</td>
</tr>
<tr>
<td>6.</td>
<td>[78]</td>
<td>2013/2011</td>
<td>47/F</td>
<td>UP</td>
<td>IC</td>
<td>Fever, vomiting, dysphagia, altered sensorium, papules on trunk, extremities, labia minora, soft palate, hypercalcemia</td>
<td>Skin biopsy</td>
<td>Positive/Positive</td>
<td>ic/cure</td>
</tr>
<tr>
<td>7.</td>
<td>[79]</td>
<td>2012/2012</td>
<td>4/M</td>
<td>nk</td>
<td>ID (aplastic anemia)</td>
<td>Febrile neutropenia, large focal lesions in liver on ultrasound</td>
<td>Ultrasound-guided liver biopsy</td>
<td>Positive/not done</td>
<td>amB+ vor*/Death</td>
</tr>
<tr>
<td>8.</td>
<td>[80]</td>
<td>2012/nk</td>
<td>62/M</td>
<td>nk</td>
<td>IC</td>
<td>Fever, weight loss, anorexia, bilateral adrenal enlargement</td>
<td>Adrenal fna</td>
<td>Positive/positive</td>
<td>amB/improvement</td>
</tr>
<tr>
<td>9.</td>
<td>[80]</td>
<td>2012/nk</td>
<td>52/M</td>
<td>nk</td>
<td>IC</td>
<td>Fever, weight loss, anorexia, bilateral adrenal enlargement</td>
<td>Adrenal fna</td>
<td>Positive/positive</td>
<td>amB/improvement</td>
</tr>
<tr>
<td>10.</td>
<td>[80]</td>
<td>2012/nk</td>
<td>61/M</td>
<td>nk</td>
<td>IC</td>
<td>Fever, weight loss, anorexia, bilateral adrenal enlargement</td>
<td>Adrenal fna</td>
<td>Positive/positive</td>
<td>amB/improvement</td>
</tr>
<tr>
<td>11.</td>
<td>[p1]</td>
<td>p/2003</td>
<td>43/F</td>
<td>UP</td>
<td>IC</td>
<td>Fever, weight loss, right upper abdomen pain,</td>
<td>BMA, Peripheral blood smear</td>
<td>Positive/positive</td>
<td>amB-ic/Cure</td>
</tr>
<tr>
<td>S. No.</td>
<td>Ref</td>
<td>Yr. of publ./ Pres.</td>
<td>Age/sex</td>
<td>State</td>
<td>IC/ID (cond.)</td>
<td>Clinical features</td>
<td>Clinical sample</td>
<td>Histopathology/culture</td>
<td>Treatment/outcome</td>
</tr>
<tr>
<td>-------</td>
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<td>-------------------</td>
</tr>
<tr>
<td>14.</td>
<td>[p4]</td>
<td>p/2012</td>
<td>60/M</td>
<td>nk</td>
<td>nk</td>
<td>nk</td>
<td>Palatal biopsy</td>
<td>Positive/positive</td>
<td>nk, Patient could not be traced</td>
</tr>
<tr>
<td>15.</td>
<td>[p5]</td>
<td>p/2013</td>
<td>40/M</td>
<td>Bihar</td>
<td>IC</td>
<td>Fever, cough, papules over body, buccal mucosa and palatal ulcer, bilateral adrenal enlargement</td>
<td>Skin biopsy</td>
<td>Positive/negative</td>
<td>amB/improvement</td>
</tr>
<tr>
<td>17.</td>
<td>[p7]</td>
<td>p/2014</td>
<td>50/M</td>
<td>UP</td>
<td>ID HIV</td>
<td>Nodulo-ulcerative skin lesion, hepatosplenomegaly, lymphadenopathy, breathlessness</td>
<td>Skin biopsy</td>
<td>Positive/positive</td>
<td>amB/death</td>
</tr>
<tr>
<td>18.</td>
<td>[p8]</td>
<td>p/2014</td>
<td>47/M</td>
<td>Bihar</td>
<td>IC</td>
<td>Nodulo-ulcerative skin lesion, hepatosplenomegaly,</td>
<td>Skin biopsy</td>
<td>Positive/positive (M-genePCR using primers MSP2F and 2R positive)</td>
<td>amB and itraconazole/ death</td>
</tr>
<tr>
<td>19.</td>
<td>[p9]</td>
<td>p/2015</td>
<td>47/M</td>
<td>Northeast</td>
<td>ID methotrexate therapy</td>
<td>Laryngeal nodule, nodulo-ulcerative skin lesion, gastrointestinal lesion</td>
<td>Laryngeal nodule and skin biopsy</td>
<td>Positive/not done</td>
<td>amB and IC/ improvement</td>
</tr>
<tr>
<td>20.</td>
<td>[p10]</td>
<td>p/2015</td>
<td>40/M</td>
<td>UP</td>
<td>IC</td>
<td>Fever, hepatosplenomegaly, palatal and naso-pharyngeal ulcer</td>
<td>Palatal ulcer biopsy</td>
<td>Positive/positive (M-genePCR using primers MSP2F and 2R positive)</td>
<td>amB and IC/ Improvement</td>
</tr>
</tbody>
</table>

Ref reference, Publ. publication, Pres. presentation, IC immunocompetent, ID immunosuppressed, cond. condition of immunosuppression, nk not known, M male, F female, fna fine needle aspiration, amB amphotericin B, ic itraconazole, vor voriconazole, CT computed tomography, UP Uttar Pradesh, BMA bone marrow aspirate, (p) present study. * indicates followed by, + indicates along with
was given in 57 cases (Table 3). Important suggestive occupational exposure in these patients included agricultural work, exposure to birds, construction site related exposure, forest worker, wood cutter, where exposure to soil would have been a possibility. Notably, of these, 17 (55%) had a history of agriculture-related work and 9 (32%) had a history of exposure to birds.

Geographical location: Data regarding the actual state of residence and the institutes from where the cases were published are shown in Table 4 and Fig. 4.

History of travel to other countries was known for 2 cases [10, 52].

Underlying disease and predisposing factors: Of 214 cases, 70 (32.7%), had history of underlying immunosuppression. Details of various reasons for immunosuppression are given in Table 5. Infection with HIV was the commonest underlying condition, being responsible for approximately 72% of immunocompromised cases followed by renal transplantation with immunosuppressive therapy (approximately 11% of cases of immunosuppression.) Among HIV cases,
Clinical features: Of 214 cases of disseminated histoplasmosis reported within the study period, twenty cases presented to various clinics of our institute (Table 1). Detailed clinical features were available for 213 cases (Table 2) as one case who presented to outpatient department of our institute (p4, Table 1) could not be traced. Comparison of clinical and demographic features for immunocompromised and immunocompetent cases is also provided in Table 2. Of all cases, seven patients had single organ involvement, of which, 5 involved gastrointestinal tract and one each involved brain and epididymis.

Diagnostic Modality: Histopathology or direct demonstration from the clinical sample was positive in all. Microbiological culture was attempted in 106 cases (106/177, i.e., 57%) (we excluded 37 patients from the study by Deodhar et al. [53] since the total number of samples subjected to culture was not mentioned) and *H.*
capsulatum grew in 64 (60%) cases. Two studies confirmed H. capsulatum grown in culture by molecular methods [33, 54]. Serological testing by Immunodiffusion was done in 3 studies [10, 55, 56], of which 2 mentioned positive [10, 55] results. Anti-histoplasma antibody detection from serum by immunodiffusion was done 4 of our patients (p7, p8, p9 and p10), of which three tested positive (p7, p8, p9; Table 1).

Table 3  Occupational history with respect to disseminated histoplasmosis in published cases from India in twenty-first century (includes unpublished cases from our hospital; \( N = 57 \))

<table>
<thead>
<tr>
<th>Occupational history significant for histoplasmosis</th>
<th>Number of cases = 31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farmer or agriculture related</td>
<td>17</td>
</tr>
<tr>
<td>Exposure to birds</td>
<td>10</td>
</tr>
<tr>
<td>Construction worker</td>
<td>1</td>
</tr>
<tr>
<td>Wood cutter</td>
<td>1</td>
</tr>
<tr>
<td>Grain factory worker</td>
<td>1</td>
</tr>
<tr>
<td>Forest officer</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
</tr>
<tr>
<td>Occupational history not significant for histoplasmosis</td>
<td>No. of cases = 26</td>
</tr>
</tbody>
</table>

Table 4  Distribution of published cases in twenty-first century from each Indian state (includes unpublished cases from our hospital)

<table>
<thead>
<tr>
<th>State</th>
<th>Cases reported with definitive history of residence in a state</th>
<th>Number of cases reported from each state*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uttar Pradesh</td>
<td>11</td>
<td>24</td>
</tr>
<tr>
<td>Bihar</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Delhi</td>
<td>2</td>
<td>33</td>
</tr>
<tr>
<td>Haryana</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Jharkhand</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Chandigarh + Punjab</td>
<td>0</td>
<td>19</td>
</tr>
<tr>
<td>North India*</td>
<td>19 (27%)</td>
<td>90 (52%)</td>
</tr>
<tr>
<td>West Bengal</td>
<td>25</td>
<td>31</td>
</tr>
<tr>
<td>Assam</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Tripura</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Manipur</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Meghalaya</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Northeast India</td>
<td>37 (51%)</td>
<td>43 (25%)</td>
</tr>
<tr>
<td>Madhya Pradesh</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Chhattisgarh</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Rajasthan</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Gujarat</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Maharashtra</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Central India*</td>
<td>6 (8%)</td>
<td>19 (11%)</td>
</tr>
<tr>
<td>Karnataka</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Andhra Pradesh</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Tamil Nadu</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Kerala</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>South India*</td>
<td>10 (14%)</td>
<td>27 (16%)</td>
</tr>
<tr>
<td>Total</td>
<td>72</td>
<td>179</td>
</tr>
</tbody>
</table>

* Regional zone was mentioned in the original article, 2 each for North and South India and 1 from Central India

* Total number of cases reported from the institutes located and cases with definitive history of residence in a particular state.
Treatment and outcome: A history of treatment given was mentioned for 183 cases; detailed analysis of specific antifungals given and response to treatment is given in Table 6. Final outcome data were available for 166 cases, of which, 130 (78%) reported an improvement or cure and 23 (14%) died. Thirteen cases relapsed on giving the primary therapy, mainly azoles, of which four improved on changing the treatment. The mortality was significantly higher in immunocompromised cases when compared to the immunocompetent cases (27.5% (14/51) vs. 10% (9/90), \( p = 0.01 \), Fisher’s exact test) (Table 2).

Adrenal histoplasmosis: Adrenal involvement was noted in 74 (35%) cases, of which a diagnosis of adrenal histoplasmosis was reported in 49. The mean age of presentation was 54.4 ± 12.3 years (range 31–83, median 55, data available for 35/74). All cases were reported in male patients except one [57], and all were immunocompetent. A history of the presence or absence of adrenal insufficiency was mentioned in 56 cases, of which, 20 (35.7%) had features of adrenal insufficiency.

Discussion

We observed an upward trend in reporting of cases of histoplasmosis from India in this century (Fig. 2). Till previous review in 1994 [8], there were only 37 authentic cases of histoplasmosis reported from India.
We noted a pronounced increase in reported cases in the last 4 years wherein, more than 50% of cases had been published (Fig. 2; 48 single- or double-case reports published between 2012 and 2015 compared to 18 from 2002 to 2008). Even, of 20 cases from our institute, 14 (70%) were either published or diagnosed in last 5 years. It may be attributed to the combination of factors like increase in awareness among treating or diagnosing physicians regarding the disease, increase in awareness to publish the diagnosed cases or increasing contact of humans to the pathogen due to increasing excavation of soil due to urbanization.

Table 5 Various reasons for underlying immunosuppression in published cases (includes cases presented in the present study)

<table>
<thead>
<tr>
<th>Underlying disease or predisposition</th>
<th>Number of cases reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV/AIDS</td>
<td>39 (72.3%)</td>
</tr>
<tr>
<td>Renal transplant (on immunosuppression)*</td>
<td>6 (11.2%)</td>
</tr>
<tr>
<td>Immunodeficiency syndromes*</td>
<td>4 (7.4%)</td>
</tr>
<tr>
<td>Bladder carcinoma (post-intravesical BCG)</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>Hairy-cell leukemia</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>Oral steroids</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>Rheumatoid arthritis under immunosuppressive therapy</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>N = 54</td>
</tr>
</tbody>
</table>

Although a total of 65 patients with immunosuppression were included in the study, data regarding the etiology of immunosuppression of 11 patients with immunosuppression were not provided in the study by Deodhar et al. [46]

* Five patients were on immunosuppressive regimen at the time of diagnosis (3 on triple drug induction regimen and 2 on maintenance regimen, all were on oral prednisolone)

* One patient each of Idiopathic CD4 T-cell lymphocytopenia and Job’s syndrome and 2 patients with pancytopenia

Table 6 Antifungal treatment given in published cases and their response to treatment (includes cases presented in the present study)

<table>
<thead>
<tr>
<th>Antifungal treatment</th>
<th>Number of patients*</th>
<th>Response to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole only</td>
<td>82</td>
<td>34 I/C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 R</td>
</tr>
<tr>
<td>Amphotericin B only</td>
<td>24</td>
<td>9 I/C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 D</td>
</tr>
<tr>
<td>Amphotericin B followed by itraconazole</td>
<td>60</td>
<td>24 I/C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 D</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 R</td>
</tr>
<tr>
<td>Fluconazole only</td>
<td>5</td>
<td>1 I/C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 switched to amB-IC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 lost to follow-up</td>
</tr>
<tr>
<td>Amphotericin B with voriconazole</td>
<td>1</td>
<td>1 D</td>
</tr>
<tr>
<td>Amphotericin B with fluconazole (given for cryptococcal meningitis)</td>
<td>1</td>
<td>1 I/C</td>
</tr>
<tr>
<td>Ketoconazole alone</td>
<td>1</td>
<td>1 I/C</td>
</tr>
<tr>
<td>Voriconazole alone</td>
<td>1</td>
<td>1 I/C</td>
</tr>
</tbody>
</table>

Number includes patients where outcome is not known

I/C improved/cured, D Death, R relapse, amB-IC Amphotericin B followed by Itraconazole
Overall, we found that nearly half of reported cases in whom occupational history was available occurred in people who engaged in farming or agriculture-related activities (Table 3) and belonged to the rural setting. Additionally, a history of exposure to birds, either as a pet or having residence near poultry farm, was mentioned for 12% cases with recorded occupational history. A similar association has been noted from other developing countries [57], which is in contrast to USA where most cases are reported in people engaged in recreational activities such as spelunking [1]. However, it needs to be interpreted with caution as India traditionally being an agricultural country with three-fourths of its population living in rural setup, it is likely that more cases with such background are reported. This underscores the utility of screening for histoplasma infection in Indian subjects with potential of exposure. For prevention of infection, Centre for Disease Control (CDC) has recommended usage of wetting agents to decrease the generation of aerosolized dust, wearing personal protective equipment like National Institute for Occupational Safety and Health (NIOSH)-approved respirators, exclusion of birds and bats from buildings and places where excavation activity is going to occur. These means are particularly important for immunocompromised subjects involved in agricultural or farming activity as inhalation exposure to organisms like Cryptococcus spp. or Chlamydia psittaci can also be avoided [58].

In the present review, it was observed that about three-fourth of cases published in the present century were reported from institutes located in northern and northeastern states of India, namely Uttar Pradesh (UP), New Delhi, Haryana, Punjab, West Bengal, Assam and Bihar which form the plains of 3 major rivers in north India, namely Ganges, Yamuna and Brahmaputra (Fig. 4), similar to the findings of previous reviews [7, 8]. The actual state of residence was mentioned for only about 33% cases (72/214) in our analysis (Table 4). With increasing migration of people, this cannot be entirely relied upon to delineate the zones of endemicity of the disease.

Skin sensitivity to histoplasmin antigen is an epidemiologic tool to determine the geographical distribution of infection, and study conducted about 50–60 years back had found high rates of reactivity among people living in districts situated along the banks of rivers Ganges and Yamuna [59]. Unfortunately, no recent study is available from India to determine the endemic zones of infection and the burden of asymptomatic infection. Even, attempts to isolate H. capsulatum from soil in various parts of India [60] and bat habitats [61] have been unsuccessful barring one soil sample along river Ganges [60]. The major soil type in India is alluvial soil which is present along the banks of rivers Ganges, Yamuna and Brahmaputra in north and Godavari, Krishna and Cauvery in south. This soil is highly fertile though poor in organic and nitrogenous contents [62]. This could be the reason for the absence of isolation of H. capsulatum from soil samples along these rivers as the fungus usually grows in acidic soil with high nitrogen content [63]. Thus, we hypothesize that this alluvial soil present in majority of plains in India is not supportive for the growth of H. capsulatum. However, with rise in the number of reported cases of histoplasmosis, the ecological niche for the organism should be further looked into using sensitive molecular detection methods. However, in the present analysis, of all patients with disseminated histoplasmosis having a significant occupational exposure, majority had contact to soil with respect to farming (55%) or exposure to birds (32%), both of which can be the major ecological niche in our country.

As reported previously [6–8], we noted a strong gender predisposition toward male gender as male-to-female ratio was 6:1. Studies world-over have also noticed this peculiar association [64, 65] and in Indian population this is quite apparent. In our analysis, involvement of male gender was significantly higher when compared to published studies from China [64] and USA [65] (86 vs. 71 and 66%, p = 0.0001 each, Fisher’s exact test). Although the skin reactivity to histoplasmin antigen does not show a gender predisposition in some studies, [66, 67] we suspect that more chances of occupation-related exposure to soil or dust result in increased rate of infection in Indian males. However, a study has attributed to the protective role of β-estradiol in women against histoplasmosis as this hormone has to affect the mycelial-to-yeast transition and also seems to increase the secretion of Th1 cytokines like interferon-γ [54].

As reported from other countries [64, 65, 68], our findings show that histoplasmosis is primarily a disease of middle-aged persons in India as about two-third to three-fourth of cases in our analysis affected people from 4th to 6th decades of life. A
significant finding of compilation of data from all studies from India regarding disseminated histoplasmosis in this century was the fact that the mean age of the immunocompromised patients (37.9 ± 14.0 years (range 4–70)) was significantly lower than the mean age of the immunocompetent patients with disseminated histoplasmosis [49.2 ± 14.9 years (range 3–83)]. Among all adult cases from our institute, the mean age of immunocompromised patients (mean age 45.0 ± 12.1 years) was lower than that of immunocompetent subjects (mean age 49.9 ± 8.1 years), although not statistically significant. The ratio of immunocompetent to immunocompromised patients with disseminated histoplasmosis was similar in cases from all over India as well as the cases from our institute (1.83:1 and 1.37: 1, respectively). The association of immunosuppressive diseases, most commonly HIV-infection, with disseminated histoplasmosis in younger adults, makes it mandatory for screening for HIV-infection, particularly in the age group of patients of 21–40 years of age. Lower mean age in immunocompromised patients can be due to primary infection disseminating in the initial phase of infection in immunocompromised cases, whereas immunocompetent cases may have endogenous reactivation which presents at a later stage of life, as observed in tuberculosis [69].

Although the review focuses on disseminated histoplasmosis in India, during literature search we found only 6 reported cases of pulmonary histoplasmosis published during the last 15 years, similar to the findings of previous reports from India [7, 9] and other developing countries [64, 68]. This could be due to undiagnosed initial pulmonary infection, which is either asymptomatic or mildly symptomatic. Underutilization of serological testing could be a factor although both antigen and antibody detection assays are useful in diagnosis of acute pulmonary histoplasmosis. [68]. In our view, a large number of cases of histoplasmosis especially pulmonary are being misdiagnosed due to similar clinical presentations and high prevalence of tuberculosis in India. A majority of the cases might be getting misdiagnosed as sputum negative pulmonary tuberculosis as the radiological picture is often similar. Hence, in the absence of utilization of these diagnostic modalities, we assume that the burden of pulmonary histoplasmosis in India could be much greater than what has been reported till now, which has actually led to the increase in the burden of disseminated disease in the susceptible population.

In our analysis, there was a significantly higher occurrence of clinical lymphadenopathy and mucocutaneous manifestations in immunocompromised cases and weight loss in immunocompetent cases (Table 2). The higher occurrence of cutaneous lesions in HIV patients has been reported previously [70, 71] and nearly, three-fourth of immunocompromised cases in our analysis were HIV positive (Table 5). It may be due to genetic variations in the prevailing strains of H. capsulatum in India. Although South American [class 5 or 6 Restriction Fragment Length Polymorphism (RFLP)] strains are known to be associated more with cutaneous manifestations than the North American (RFLP class 2) strains, no study from India is available on the molecular typing of H. capsulatum strains [71].

A stark finding in the study was that adrenal involvement was significantly higher in immunocompetent cases. A similar observation was reported from Brazil, wherein HIV-positive cases did not have adrenal involvement [68]. Furthermore, adrenal involvement has been described mainly in immunocompetent patients from other parts of world also [72, 73]. However, adrenal involvement was ruled out by either ultrasonography or computed tomography of abdomen in 33 (51%) of 65 immunocompromised cases and 95 (80%) of 119 immunocompetent cases. Similarly among cases from our institute, the percentage of patients with adrenal involvement was higher in immunocompetent subjects compared to immunodeficient ones (54.5 vs. 0%). Reasons for this association could be due to inability to mount an immune response to form granuloma which usually leads to destruction of adrenals [73] or the clinical presentation in them is usually acute to fulminant, wherein the features of adrenal involvement have not manifested yet.

The overall mortality rate was 14% among cases for whom outcome data were available. In our hospital, outcome was favorable in 13 (68%), while death occurred in 3 (26%) of 15 cases. Overall, our findings are in concordance with what has been reported from India, till now. Thus, there has been a reduction in the mortality rates when compared to the previous reviews [7, 8] from India but comparable to reviews from China [64] and USA [65]. However, the period of follow-up was variably reported in these reports. Most cases responded well to therapy, and an improvement or cure was achieved in 78% cases. A majority of

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reported cases received oral itraconazole (45%) as the specific antifungal therapy, and no deaths were reported in them. There were reports of relapse in 5 cases who received oral itraconazole, but the duration of therapy was not known in them. Amphotericin B was given as initial drug in about 47% of cases owing to the severity of disease. Of these, 28% received amphotericin B only, 69% received oral itraconazole thereafter and 1 case received voriconazole along with amphotericin B. A high mortality (30%, 15/30) was observed in cases who received amphotericin B as initial antifungal drug which is likely due to the severity of illness at presentation.

Our study has some limitations. Firstly, disease incidence and prevalence cannot be estimated as there is great variability in the underlying population. Secondly, a publication bias is a major limitation as most cases were published from the point of view of presenting a rare case. Thirdly, we encountered variability in reporting of clinical data as certain findings may have been overemphasized to make the clinical case interesting or omitted to limit the presented case. Furthermore, publication of case reports is fraught with many variables such as, experience and interest of diagnosing or treating physicians, the presence of an unusual occurrence or absence of a usual feature and interest of the publishing journal. Thus, institutes from where cases are reported; academic or non-academic; government or privately funded and availability of specialized laboratories for mycological diagnosis can have an influence on our findings. Also, in the absence of a control group, the causality of certain associations cannot be established. Nevertheless, in the absence of well-designed, systematic studies from India, this study may help us in understanding the epidemiology of histoplasmosis in detail and pave way for future analytical studies.

As of now, few studies from India have analyzed the occurrence of histoplasmosis retrospectively for more than 5 years [18, 33, 54, 74, 75]. Some analyzed the whole spectrum of cases [18, 54, 74] presented to them, whereas others specifically looked into select patient population [33, 75]. The largest case series which analyzed all cases diagnosed over a decade presented 37 cases of disseminated histoplasmosis [53]. Even in our own experience, we encountered only 20 cases over 15 years (Table 1), all of which are either published or presented in this study. With rise in reported cases in the last 5 years, it can be concluded that occurrence of disseminated histoplasmosis has increased in India in the current decade, although no studies ever looked at the actual burden of infection in the community setting.

Conclusions

In India, histoplasmosis is largely a disease of middle-aged, male patients. It is reported mainly in people living in rural setting, who engage in agriculture or related activities leading to higher exposure to soil or dust. The disease is mainly extrapulmonary though large number of pulmonary histoplasmosis may be getting missed due to asymptomatic or milder symptomatology or getting misdiagnosed due to lack of available diagnostic facilities. Hence, high clinical suspicion and awareness regarding the pathogen is required on the part of treating physician and considerable experience on the part of histopathologists and microbiologists.

The environmental niche of the fungus and burden of infection in the community remains largely unexplored in India, although it is likely that the soil in India is not supportive to its growth and fungus may be present only in low inoculum. The geographical distribution and general epidemiology of histoplasmosis remain largely unchanged in India from what was known previously. However, it needs to be highlighted that younger adults with disseminated histoplasmosis in the age group of 21–40 are more frequently associated with immunosuppressive diseases like HIV-infection and needs to be screened once diagnosed with histoplasmosis. However, overall number of cases being reported are increasing which could be attributed to increasing awareness regarding the pathogen itself while treating or diagnosing; an increase in awareness toward publication of identified cases; an increase in the survival of immunodeficient patients or due to increasing urbanization causing excavation of infested soil leading to aerosolization of infective forms and subsequent infection of those who work in such environment. With a high burden of Indian population involved in agricultural and farming activity, protective measures like usage of wetting agents to decrease dust generation, respirators and exclusion of birds or bats from high-risk sites can be helpful.
keeping in mind that this population remain unscreened for their immune status.

Compliance with Ethical Standards

Conflict of interest  The authors declare that they have no conflict of interest.

References


