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Research Article

Histoplasmosis in Sri Lanka – barely recognized, yet present

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Abstract
Histoplasmosis has been reported in Sri Lanka for decades; however, clinical recognition and diagnosis of the disease are rare. We conducted a comprehensive search of English-language medical literature from 1969 to February 2022. Our analysis found one population survey of histoplasmin skin sensitivity testing in 1969 (5.7% positive incidence) and ten cases of histoplasmosis across Sri Lanka. The highest number of cases were reported from the Central province, where the positive histoplasmin tests were observed previously. None of the patients were positive for HIV, and both diabetes and betel chewing seem linked with oral histoplasmosis. Out of the reported cases, 50% were diagnosed with disseminated histoplasmosis; asymptomatic, acute pulmonary, and chronic pulmonary histoplasmosis were not observed. The clinical presentation varied from oral lesions (the most common presentation), skin lesions, and fever of unknown origin to adrenal crisis. Fungal culture and histopathology were used for diagnosis, with no use of antigen and antibody testing. Amphotericin B and itraconazole were used as treatment options. The rising at-risk population mandates enhancing laboratory diagnostic facilities and increasing the awareness of medical professionals in Sri Lanka on histoplasmosis.

Keywords: Ceylon, Diagnosis, Fungi**,** *Histoplasma capsulatum*, Histoplasmin, Mycosis

1. Introduction
Histoplasmosis is a systemic endemic mycosis caused by *Histoplasma capsulatum* complex. These are dimorphic fungi that exist as molds at room temperature (25–30 °C) and transform into budding yeast cells at

human body temperature (37 °C) (Develoux et al. 2021). Histoplasmosis can occur in both immunocompetent and immunocompromised individuals. However, patients with underlying immunodeficiency are more susceptible to severe forms of the disease (Scully and Baddley 2018). Patients with human immunodeficiency virus (HIV) and a cluster of differentiation 4 (CD4) cell count below 100 cells/µL are particularly prone to severe histoplasmosis, and the mortality rate of HIV-associated histoplasmosis ranges from 10% to 60% (Limper et al. 2017). Since 1987, disseminated histoplasmosis has been recognized as an acquired immunodeficiency syndrome (AIDS)-defining infection and may be the first AIDS-related infection diagnosed in newly infected HIV patients (Armstrong-James et al. 2014, Limper et al. 2017). In addition to HIV, severe disseminated histoplasmosis is observed in patients with hematological malignancies, solid organ or stem cell transplants, individuals on immunosuppressive therapy, and even among the pediatric population (Scully and Baddley 2018, Ekeng et al. 2021).

Histoplasmosis is well known to be endemic in certain geographic regions (such as the Americas). However, its global distribution is much wider, including most South East (SE) Asia and many parts of Africa (Oladele et al. 2018, Baker et al. 2019, Zhou et al. 2020). In SE Asia, there is a substantial mismatch between areas of prior exposure, many of which are hyperendemic for histoplasmosis and diagnosed cases (Baker et al. 2019). The known geographic spans of pathogenic fungi including *Histoplasma* spp. are spreading into new territories due to climatic changes. For example, hurricanes, floods, storms, and other extreme weather conditions associated with climate change disperse the ecological niches of fungi leading to the aerosolization of fungal spores into new areas (Nnadi and Carter 2021). An increasing number of cases have been observed following extreme weather and disruption of the natural ecological niche of *Histoplasma* spp. This is a known risk factor associated with outbreaks. The higher growth of *Histoplasma* spp. is observed in soil with high humidity where such regions linked with climatic changes might allow the organism to thrive. In addition, climatic changes leading to changes in soil pH, altered distance to open water, and changes in land cover could affect the geographical distribution of *H. capsulatum* complex (Gadre et al. 2022). Climate change affects all aspects of the ecosystem including animals. The behavioral changes of bats and birds linked with climatic changes might have a repercussion on the dispersion of spores of *H. capsulatum* (van Rhijn and Bromley 2021).

In the absence of proper awareness about reported cases, there may be a general belief that histoplasmosis is a non-existent or an extremely rare condition in Sri Lanka, and other parts of SE Asia and Africa. Recently published data from West Africa shows that disseminated histoplasmosis in AIDS was more common than cryptococcal meningitis in Ghana and more frequent than tuberculosis in parts of Nigeria (Ocansey et al. 2022, Oladele et al. 2022). Here, we present the results of a retrospective analysis of histoplasmosis cases reported in Sri Lanka from 1969 to 2022. We delineate the distribution, predisposing conditions, clinical presentations, diagnostic methods, management, and outcome of histoplasmosis cases in the country. The aim of this narrative review is to raise awareness among clinicians about the existence of this treatable condition in Sri Lanka and other regions with few clinical diagnoses of histoplasmosis.

2. Materials and Methods

We carried out a comprehensive search of medical literature in the English language through PubMed and Google Scholar databases in February 2022. Our search terms were "*Histoplasma capsulatum'*, "histoplasmosis", "histoplasmin" and "Sri Lanka", with the period ranging from 1969 to February 2022. In addition, abstracts from the local proceedings of conference databases were also assessed. Either culture-proven or histopathologically proven cases were selected as diagnostically confirmed histoplasmosis. Duplicate reports were excluded. All available data on demography, clinical presentation, diagnostic method, management, and clinical outcome were appraised for the reported cases.

3. Results

Epidemiological and clinical information related to histoplasmosis in Sri Lanka remains inadequate and fragmented because details of these patients were frequently dispersed through local journals or abstracts from the local proceedings of conferences. Our comprehensive search of medical literature in English language

from 1969 to 2022 identified one survey of histoplasmin skin sensitivity testing and ten cases of histoplasmosis across Sri Lanka, reported in three abstracts and eight journal articles published over a period of 53 years.

The oldest evidence of histoplasmosis in Sri Lanka was a survey of histoplasmin sensitivity among 1366 Sri Lankan volunteers in 1969. Christopher Gunapala Uragoda (previous joint editor of the Ceylon Medical Journal) and colleagues recruited 524 males and 842 females from areas of Western and Central provinces of Sri Lanka and revealed 5.7% positive reactions (Uragoda et al. 1971). Thereafter, histoplasmosis has been reported in these and other areas of the country.

The first case of histoplasmosis in Sri Lanka was reported by Jayaweera et al. (1975). It was followed by nine more cases over the past five decades (Table 1). The majority of the patients were male (90%) with the mean age of 48 years (24Y-66Y). This pattern might be explained by their outdoor occupations and recreational activities exposing them to fungal spores. The gender and age distribution were in line with the hitherto published data and showed that the disease is more prevalent among middle-aged males (Patel et al. 2018, Rajbhandari et al. 2019). Although we have not come across any pediatric cases, a report on pediatric histoplasmosis in endemic countries is available as contrary evidence (Ouellette et al. 2019). Reports show many histoplasmosis cases in children with underlying conditions such as malignancies, organ transplantation, and malnutrition (Ekeng et al. 2021). The high degree of clinical suspicion combined with sophisticated diagnostic techniques used in these countries allowed the detection of pediatric cases (Ouellette et al. 2019).

Table 1. Demographic features of the patients

Case No.	Reference	Age/ Gender	Province in Sri Lanka/ Country	Occupation	Possible exposure history and associated conditions
1	Jayaweera et al. (1975)	53/M	Eastern province	Farmer	Accidental injury with a stick he used to drive buffalo 2 years before
2	Harten et al. (1994)	24/F	Germany	Not mentioned	Previously healthy
3	Karunanayake et al. (2009)	30/M	Central province	Bodybuilding coach	Non-Hodgkin lymphoma
4	Vidanagama et al. (2010)	59/M	Southern province	Farmer	Betel chewer, alcoholic, diabetes mellitus
5	Dhammika et al. (2017)	35/M	Southern province	Farmer	Used to sleep in the bat cave, betel chewer, alcoholic
6	Jayawardena et al. (2019)	66/M	Sabaragamuwa province	Labourer	Betel chewer, smoker, diabetes mellitus
7	Sigera et al. (2020)	56/M	Central province	Vegetable seller	Betel chewer, smoker, diabetes mellitus, COPD
8	Keragala et al. (2020)	56/M	Not mentioned	Labourer	Not mentioned
9	Jayathilake et al. (2020)	42/M	Central province	Grocery shop owner	Smoker, diabetes mellitus
10	Prashanthi et al. (2021)	60/M	Not mentioned	Kandyan dancer	Exposure to birds in caves

3.1 Suitable ecological niche

Three of the patients had clear evidence of a travel history (Harten et al. 1994, Karunanayaka et al. 2009, Prashanthi et al. 2021) and one of them was a female of European origin who had traveled to several countries (Harten et al. 1994). However, the authors infer that her infection was probably acquired during her visit to Sri Lanka, as there was a long interval after visiting those countries. Three of the patients had never traveled outside Sri Lanka (Jayaweera et al. 1975, Jayathilake et al. 2020, Sigera et al. 2020), and four were unlikely

to have traveled outside Sri Lanka (Vidanagama et al. 2010, Dhammika et al. 2017, Jayawardena et al. 2019, Keragala et al. 2020). Consequently, approximately 80% were probably indigenous cases, supporting a likely local environmental niche for *H. capsulatum*. Histoplasmosis was reported in the Central province (Karunanayaka et al. 2009, Jayathilake et al. 2020, Sigera et al. 2020), Southern province (Vidanagama et al. 2010, Dhammika et al. 2017), Eastern province (Jayaweera et al. 1975) and Sabaragamuwa province (Jayawardena et al. 2019) (Figure 1). It is noteworthy that most of the reported cases have occurred in Central province where the previous skin positivity for histoplasmin was documented. We surmise that Dr. Uragoda was stimulated to do the histoplasmin skin survey because he had seen cases of histoplasmosis, which were never reported.

Inhalation of microconidia of *H. capsulatum* mold from the environment is the means of acquiring the disease (Staffolani et al. 2018). Sri Lanka is an island located in the Indian Ocean and has rich biodiversity and a warm tropical climate that provides various ecological niches suitable for *H. capsulatum* complex. The mold form of *H. capsulatum* thrives in soil contaminated with bat and avian excreta which contain a high level of nitrogen. Consequently, bats (Chiroptera) and birds are usually the subjects of discussion when it comes to histoplasmosis. Bats can get infected with *H. capsulatum* complex and they disperse the fungus in their excreta which mount up within caves and under roosting trees. Unlike bats, birds are immune to *H. capsulatum*. However, they promote fungal growth in soil by nourishing the soil with their waste rich in phosphorus and nitrogen (Diaz 2018). Consequently, exposure to infective propagules can occur in places where bird or bat droppings get disturbed (Armstrong et al. 2018, Diaz 2018). Stream banks, forest caves, empty buildings, chicken coops, golf courses, tennis complexes, and amusement parks in endemic areas welcome resting or roosting birds and bats and can be considered high-risk settings for acquiring histoplasmosis (Diaz 2018).

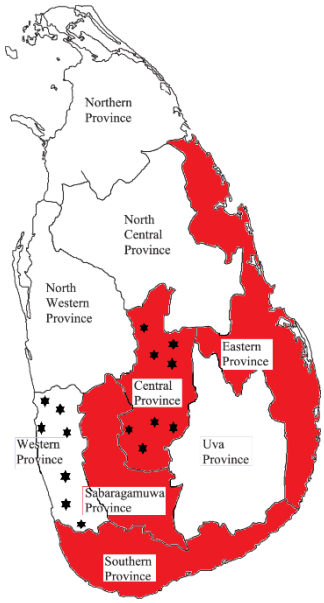

Figure 1. Map of Sri Lanka describing the distribution of histoplasmosis cases among provinces (● indicates areas in which individuals were recruited for the survey of histoplasmin skin sensitivity. Colored areas indicate areas that have reported cases of histoplasmosis, The outline of the map was downloaded from https://www.researchgate.net/figure/Provincial-Map-of-Sri-Lanka_fig1_32050368. It was colored and developed by the first author).

According to Rubsamen et al. (2004), there is a greater diversity of cave bat species in southwestern and central hills in Sri Lanka, where the optimal climate conditions prevailing in these regions support rich and quickly growing vegetation for bats. Bats are a common sight in Sri Lanka and in 2002, thirty bat species were found to inhabit Sri Lanka (Yapa 2018). Bats roost in huge trees in rural and semi-urbanized regions, especially along riverbanks or in caves in forests (Kudagammana et al. 2013, Yapa 2018). The great diversity

of bat species and cold humid conditions along with less sunlight in the Central province may provide an ideal ecological niche for *H. capsulatum* complex. The published information related to the isolation of *H. capsulatum* from environmental samples of Sri Lanka is scarce. Detection of *H. capsulatum* in environmental samples in a laboratory setting is challenging and a study conducted by Kudagammana et al. (2013) on environmental samples (including bat guano) obtained negative results.

3.2 Occupations and activities related to exposure risk

The evidence of risk behaviors and exposure was noted among a few of the patients. Risk behaviors for histoplasmosis include occupation, residency, and traveling in specific settings in endemic areas. Individuals in endemic regions who are involved in agriculture, hunting, farming, and forestry and exposed to soil containing *H. capsulatum* complex microconidia carry a risk of acquiring histoplasmosis (de Perio et al. 2021). Other known high-risk behaviors include construction, evacuation, demolition, excavation, and renovation of buildings in endemic regions because these activities disrupt soil or plant matter containing *H. capsulatum* complex. Exposures can also occur during activities such as removal and burning of bamboo, poultry farming, and pot planting using guano-containing soils (Diaz 2018).

Occupation-related exposure was observed among five patients of whom three were farmers (Jayaweera et al. 1975, Vidanagama et al. 2010, Dhammika et al. 2017) and two were labourers (Jayawardena et al. 2019, Keragala et al. 2020). Interestingly, four out of five patients with oral lesions were betel chewers (Vidanagama et al. 2010, Dhammika et al. 2017, Jayawardena et al. 2019, Sigera et al. 2020) and three of them were smokers (Jayawardena et al. 2019, Jayathilake et al. 2020, Sigera et al. 2020). Although this cannot be clearly related to histoplasmosis, unwashed betel leaves and other local ingredients might have been contaminated with infectious propagules. One patient relates the onset of his condition to an accidental injury with a stick he used to drive buffaloes, two years prior to the onset of his oral lesions (Jayaweera et al. 1975). Localized lesions after traumatic inoculation have rarely been reported (Esquibel et al. 2017). Exploration of bat caves or their entrances, disturbance of nesting birds or bats, or their droppings are strongly associated with histoplasmosis outbreaks (Armstrong et al. 2018). Two of the patients provide a clear history of bat and bird exposure. One patient used to sleep in a bat cave (Dhammika et al. 2017) and the other had a history of exploration of caves with nesting birds (Prashanthi et al. 2021). Although it has not been identified as a risk factor among the patients, exposure to chicken coops in the poultry industry could be a risk factor in line with other settings (de Perio et al 2021, McKinsey 2021). There are more than 600,000 poultry farmers in Sri Lanka (Priyantha et al. 2022). Both indigenous and backyard chicken rearing systems, as well as commercial poultry rearing systems, are practiced. Sri Lanka observed a near doubling of the poultry population in 2017 (21.28 million chickens) compared to 2005 (11.63 million chickens). Currently, around 80% of poultry is produced primarily in six districts in Sri Lanka, including Kandy, Kurunegala, Gampaha, Puttalam, Colombo, and Kaluthara (Manjula et al. 2018). Exposure to poultry industry should be inquired about when assessing patients in the future.

3.3 Clinical presentation of histoplasmosis

The clinical manifestation of histoplasmosis is determined by the degree of exposure to infective propagules and by the host's immune status (Diwakar et al. 2015). These manifestations range from asymptomatic, acute pulmonary, and chronic pulmonary infections to more widespread disseminated infections (Folk and Nelson 2017) (Figure 2).

Asymptomatic and acute pulmonary histoplasmosis: Immune-competent individuals with primary infection may be asymptomatic or present with flu-like symptoms such as fever with or without chills, headache, nausea, vomiting, malaise, myalgias and fatigue and these symptoms usually subside without treatment and may go unnoticed (Kauffman 2007, Mary et al 2015, Diaz 2018). The severity of illness is closely linked to the magnitude of the exposure.

Chronic cavitary pulmonary histoplasmosis: Chronic pulmonary histoplasmosis may mimic other pulmonary conditions such as pulmonary tuberculosis or chronic pulmonary aspergillosis and could be misdiagnosed.

Chronic productive cough, weight loss, dyspnea and cavitary pulmonary lesions on radiology are characteristic features of chronic histoplasmosis (Baker et al. 2020).

Acute (progressive) disseminated histoplasmosis: Presents with oral lesions, skin lesions, fever of unknown origin, malaise, weight loss, constitutional symptoms, or night sweat. Pancytopenia is common. Affected people may also have physical signs of lymphadenopathy, hepatosplenomegaly, adrenal gland enlargement, and granulomatous lesions in the eyes, brain, airway, liver, and colon after hematological dissemination. Their clinical presentation usually overlaps with that of tuberculosis, and some patients with AIDS have both conditions (Mary et al. 2015).

Subacute histoplasmosis: Presents with low-grade fever, intestinal ulceration, oropharyngeal or colonic ulcerations usually with hepatosplenomegaly. Chronic disseminated histoplasmosis: Presents with intestinal and oropharyngeal ulceration. Adrenal gland involvement can be seen on imaging and hepatosplenomegaly may be detected in physical examination. Based on clinical presentation, physical findings, and investigation findings, five out of ten cases reported in Sri Lanka were diagnosed as disseminated histoplasmosis (Harten et al. 1994, Dhammika et al. 2017, Jayawardena et al. 2019, Jayathilake et al. 2020, Keragala et al. 2020). No cases of asymptomatic, acute pulmonary or chronic pulmonary histoplasmosis were observed among the reported patients in Sri Lanka. Table 2 depicts the clinical presentation and examination findings of the patients.

Non-healing oral ulcers were the most frequent presenting complaint among the patients and the appearance of these oral lesions ranged from mucosal thickening and multinodular swelling to granulomatous ulcerative lesions (Table 2). These lesions were observed in the cheek, tongue, buccal sulcus, and palate (Jayaweera et al. 1975, Karunanayaka et al. 2009, Vidanagama et al. 2010, Dhammika et al. 2017, Jayawardena et al. 2019, Sigera et al. 2020). Oral lesions are frequently observed with disseminated histoplasmosis and these are rarely seen as localized lesions without any systemic involvement (Kumar et al. 2020). Approximately 30–50% of patients with subacute disseminated histoplasmosis show oral lesions and in certain cases, oral lesions appear to be the primary diagnostic manifestation of the disseminated disease (Bhagwat et al. 2009, Pincelli et al. 2019). The appearance of mucosal lesions due to histoplasmosis can range from verrucose, nodular, plaque-like, or ulcerative lesions, and they can appear anywhere in the mouth (Diwakar et al. 2015). Two of the patients with features of dissemination presented with non-healing oral ulcers along with systemic features (Dhammika et al. 2017, Jayawardena et al. 2019). It is difficult to comment on dissemination for the remainder of the patients with oral lesions (Jayaweera et al. 1975, Karunanayaka et al. 2009, Sigera et al. 2020), because the evaluation for dissemination was incomplete. In addition, one case of an isolated oral lesion has been reported (Vidanagama et al. 2010).

Only three patients showed skin lesions (Dhammika et al. 2017, Keragala et al. 2020, Prashanthi et al. 2021) and the rate of skin involvement in the patient population appears to be less than in other settings. Their appearance ranged from generalized discrete superficial skin ulcers to erythematous plaque lesions. Two of them had systemic symptoms suggestive of dissemination (Dhammika et al. 2017, Keragala et al. 2020). Skin lesions frequently develop secondary to the dissemination of the infection and primary cutaneous lesions after direct inoculation is an uncommon presentation (Mahajan et al. 2017). The type of skin lesion due to histoplasmosis can range from papule, plaques, pustules, ulcers, nodules, acneiform eruptions, molluscum-like lesions, cellulitis, exfoliative erythroderma to abscesses. Intriguingly, the frequency and character of skin manifestation varies across the countries with the rate of skin lesions among AIDS patients in the US and Brazil being 10% and 66%, respectively (Smith et al. 2013). Interestingly, the appearance of the skin lesions in case 10 is not typical for histoplasmosis and more like leprosy lesions clinically. However, the direct smear and culture of the biopsy specimen was positive for yeast cells and *H. capsulatum* complex growth.

One case was diagnosed as acute disseminated histoplasmosis (Harten et al. 1994). This patient presented with acute severe symptoms of fever of up to 40.2°C, and transient respiratory failure that required mechanical ventilation. She was previously healthy, and her symptoms occurred shortly after a visit to Sri Lanka.

Table 2. Clinical presentation and examination findings of the patients

Case No.	Presenting complaint	Physical examination
1	Oral ulcers	Thickening of the mucosa of the right cheek, multinodular swelling underneath the anterior tongue
2	Fever up to 40.2°C, headache, weakness, nausea, and muscular pain. Transient respiratory failure requiring mechanical ventilation	Hepatosplenomegaly, generalized enlarged lymph nodes, ascites (transudate), pericardial and pleural effusions with transient respiratory failure
3	Burning sensation on swallowing, oral ulcers, and lymph node enlargement	Multiple, enlarged submandibular and submental lymph nodes with oral ulcers
4	Oral ulcers	Ulcerative lesion on upper alveolar region and hard palate
5	Oral ulcers, intermittent fever, night sweating, anorexia along with weight loss	Ulcerative growth at right upper alveolus involving palate and buccal sulcus, chronic ulcers on chest, legs, penis, a generalized skin rash
6	Oral ulcers, dysphagia of six-months duration, low-grade fever, weight loss	Pus discharging mucosal ulcer in the mid palatal region extending to the palatal aspect of the left anterior maxilla
7	Oral ulcers, odynophagia for 4 months, no fever, no weight loss	A solitary tender, irregular ulcer on the left posterior tongue with induration
8	Skin lesions, fever of unknown origin, constitutional symptoms of 3 weeks	Discrete superficial skin ulcers all over the body, no hepatosplenomegaly, no lymphadenopathy, no other systemic involvement
9	Vomiting, diarrhea, abdominal pain, and postural dizziness for three days (Addisonian crisis)	Dehydrated, postural hypotension, mild hepatomegaly, altered serum electrolytes levels
10	Skin lesions	Erythematous plaques over face and neck

One patient with disseminated histoplasmosis had adrenal involvement (Jayathilake et al. 2020). The patient, hospitalized due to an addisonian crisis, had a recent history of generalized malaise, evening pyrexia, evening sweating, severe anorexia, and weight loss. The presenting features were in line with adrenal histoplasmosis reported from other countries (Gajendra et al. 2016, Rog et al. 2016). It is observed that involvement of the adrenal gland is more common among immunocompetent individuals than among HIV patients (Singh et al. 2019). Bilateral adrenal gland involvement (enlargement on imaging) might or might not be present with adrenal insufficiency (Gajendra et al. 2016, Rog et al. 2016). Koene et al. (2013) observed that 41% of patients with adrenal histoplasmosis presented with adrenal insufficiency. The degree of adrenal gland involvement in patients with progressive disseminated histoplasmosis was 80% and 26% to 68% in autopsy series and clinical reports, respectively. Adrenal histoplasmosis might be fatal if left untreated, and a high degree of mortality has been observed in patients with both progressive disseminated histoplasmosis and primary adrenal insufficiency (Singh et al. 2019).

3.4 Diagnosis of histoplasmosis

Since the clinical presentation of histoplasmosis mimics other disease conditions, proper laboratory confirmation of the diagnosis is necessary based on microbiology (culture and direct smear), histopathology, antigen and antibody serology, occasionally molecular diagnosis (Kauffman et al. 2011) (Figure 2).

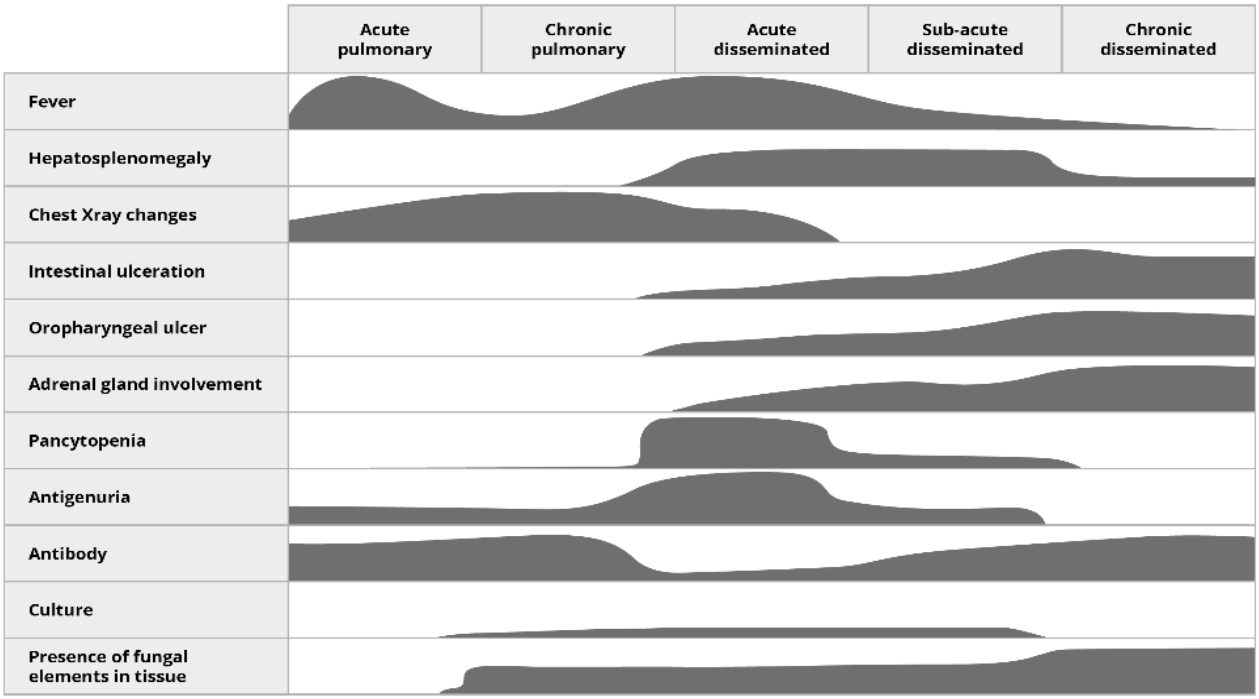

Figure 2. Clinical presentation and laboratory findings of different forms of histoplasmosis

Biopsies of oral lesions, skin lesions, adrenal mass, bone marrow and lymph nodes were investigated through direct microscopy, fungal culture, and histology. Seven out of nine biopsy specimens sent for fungal cultures provided positive results (Jayaweera et al. 1975, Karunanayaka et al. 2009, Vidanagama et al. 2010, Jayawardena et al. 2019, Keragala et al. 2020, Sigera et al. 2020, Prashanthi et al. 2021). One bone marrow biopsy culture was discarded on day 4 preventing the isolation of the slow growing *H. capsulatum* complex (Harten et al. 1994). Consequently, the culture positivity rate is approximately 78%. However, the traditional way of isolating *H. capsulatum* complex in culture hampers the early diagnosis of the disease as it requires 4 to 6 weeks of incubation (Kauffman et al. 2011). Such longer incubation periods are not routinely practiced in most laboratories, except reference laboratories for mycology, and this might be the reason behind the low positivity rate of histoplasmosis. Figure 3 shows the macroscopic (A) and microscopic (B) views of *H. capsulatum.* Since the laboratory testing of dimorphism is potentially hazardous to laboratory staff, cultures are increasingly being identified using molecular methods.

Biopsies from oral lesions (Jayaweera et al. 1975, Vidanagama et al. 2010, Jayawardena et al. 2019, Sigera et al. 2020), skin lesions (Keragala et al. 2020, Prashanthi et al. 2021) and lymph nodes (Karunanayaka et al. 2009) were culture-positive in the reported cases. Adrenal mass biopsy is infrequently positive in culture and was not observed (Jayathilake et al. 2020). All the ten biopsy specimens, oral lesions (Jayaweera et al. 1975, Vidanagama et al. 2010, Dhammika et al. 2017, Jayawardena et al. 2019, Sigera et al. 2020), skin lesions (Keragala et al. 2020, Prashanthi et al. 2021), lymph node lesions (Karunanayaka et al. 2009), adrenal mass (Jayathilake et al. 2020) and bone marrow trephine biopsy (Harten et al. 1994) sent for histopathological evaluation gave positive results. Detection of yeast form in tissue, bone marrow and blood smear with special stains such as Grocott-Gomori's methenamine silver (GMS) and Periodic Acid-Schiff stains accelerates the diagnosis of histoplasmosis (Folk and Nelson 2017). However, there is a potential for misdiagnosis, because the distinction of *H. capsulatum* from other yeasts and *Leishmania* spp. is sometimes difficult. For example, *Candida glabrata*, which lacks pseudohyphae and has a small cell size, can mimic extracellular *H. capsulatum* complex (Pan et al. 2013). Other yeasts with appearances similar to *H. capsulatum* include *Talaromyces marneffei* and *Emergomyces africanus*. Table 3 shows the culture and histopathological diagnosis of histoplasmosis cases. *Histoplasma* immunodiffusion test, complement fixation test and *Histoplasma* antigen

test were not mentioned as diagnostic tools in Sri Lanka, except in the case which was investigated and managed in Europe. However, the results were negative in this case.

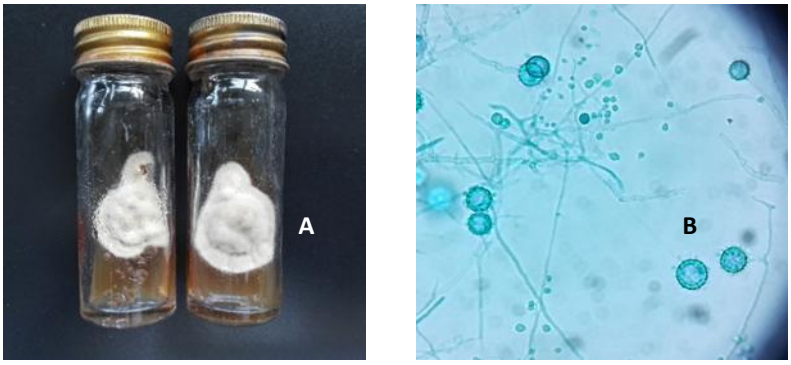

Figure 3. Macroscopic (A) and microscopic (40x) (B) views of *H. capsulatum*

Despite the lack of serological testing in Sri Lanka, there have been significant advances in this field over the last 10 years and they are routinely used in the USA. Antigen testing is a rapid diagnostic method that can also be used to assess treatment response (Kauffman et al. 2011). Antigen detection can be applied to urine, serum, Bronchoalveolar lavage (BAL) and cerebrospinal fluid (CSF); however, urine is most widely used for testing, as antigen is concentrated in urine (Azar and Hage 2017).

A study validating a new monoclonal *Histoplasma* galactomannan enzyme immunoassay among HIV patients obtained 98% and 97% of sensitivity and specificity, respectively (Caceres et al. 2018). Antigen sensitivity is highest with disseminated histoplasmosis (Libert et al. 2018) but may also be positive in acute pulmonary histoplasmosis and occasionally other forms of the disease. The sandwich Platelia *Aspergillus* enzyme immunoassay (EIA) (Bio-Rad, France) is increasingly being relied upon for the diagnosis of invasive aspergillosis (Xavier et al. 2009). This assay may yield positive results in patients with histoplasmosis (Rivière et al. 2012). For example, Wheat et al. 2007b detected galactomannan with the Platelia *Aspergillus* EIA in six patients who had culture-proven histoplasmosis and with optical density (OD) values ranging from 6.2 to 7.8 in serum (Wheat et al. 2007b). They observed that twenty-three of 48 serum specimens positive for *Histoplasma* antigen by second-generation Histoplasma EIA also became positive for *Aspergillus* galactomannan assay. Vergidis et al. (2015) reported that four solid organ transplanted patients with histoplasmosis tested positive for *Aspergillus* galactomannan. These findings indicate that the Platelia *Aspergillus* assay might be useful for the diagnosis and monitoring of treatment response of disseminated histoplasmosis (Ranque et al. 2007). Platelia galactomannan assay that is currently practiced in Sri Lanka would be a reasonable surrogate test for the diagnosis of histoplasmosis.

Histoplasma antibody tests are most suitable for the diagnosis of subacute and chronic forms of histoplasmosis (Azar and Hage 2017). Three types of serological assays, EIA, immuno-diffusion (ID), or complement fixation methods (CF) are used in *Histoplasma* antibody detection (Diwakar et al. 2015). The EIA method is the most sensitive method among the three methods and the sensitivity of CF is better than the ID method (Azar and Hage 2017).

Although there is no commercially available molecular assay for histoplasmosis, the high degree of specificity, sensitivity and low turnaround time offered by molecular testing make them more popular diagnostic methods for progressive disseminated histoplasmosis (Azar and Hage 2017). The lack of a standardized and commercialized PCR test for *Histoplasma* species complex is a barrier to implementation. Table 4 shows the sensitivity of the different diagnostic tests for histoplasmosis.

Table 3. Culture and histopathological diagnosis of histoplasmosis

Case No.	Biopsy site	Direct smear	Culture	Biopsy histopathology
1	Tongue lesion	Not mentioned	Positive	Submucosa and deeper tissue macrophages with numerous round or oval fungal bodies suggestive of histoplasmosis
2	Bone marrow	Not mentioned	discarded after 4 days	Trilinear hypercellularity with a histiocytic medullary reaction interspersed by giant cells, collagenous medullary fibrosis, demonstrated round to oval, peroxidase-positive, 3–5 g yeast cells located interstitially and in histiocytes
3	Submandibular lymph node	Positive for yeast	Positive	Intracellular yeast cells with budding forms in histiocytes, suggestive of *Candida* spp. or *Histoplasma* spp.
4	Oral lesions	Not mentioned	Positive	Dense infiltration of plasma cells, lymphocytes, macrophages, and foreign body type giant cells. Macrophages and giant cells parasitized with small ovoid yeast-like organisms indicative of oral histoplasmosis
5	Oral lesions	Not mentioned	Not mentioned	Hematoxylin and Eosin (H & E) and Periodic Acid-Schiff with diastase (PAS-D) and Grocott stain concluded granulomatous inflammation due to histoplasmosis. Biopsy of the colon mucosa demonstrated granulomatous inflammation induced by mycotic infection, consistent with histoplasmosis
6	Oral ulcer	Positive for yeast	Positive	The presence of yeast forms was suggestive of histoplasmosis
7	Oral lesion	Positive for yeast	Positive	Oral lesion biopsy positive for *Histoplasma*-like yeasts
8	Skin biopsy	Positive for yeast	Positive	Numerous plasma cells, histiocytes, lymphocytes and granulomas. Accompanying the infiltrate were numerous budding yeast forms, predominantly within histiocytes, and a few organisms residing extracellularly. Positive for *Histoplasma* species complex
9	Adrenal mass	Not mentioned	Negative	Infiltration of plasma cells and lymphocytes alone with histiocytes in adjacent tissues and fungal elements suggestive of *H. capsulatum* complex
10	Skin lesion	Positive for yeast	Positive	Granulomatous inflammation with fungal bodies suggestive of histoplasmosis

Table 4. The sensitivity of the diagnostic tests

Test	Acute pulmonary	Subacute pulmonary	Chronic pulmonary	Disseminated	Reference
Culture	0–42%	9–82%	65–85%	74–92%	Hage et al. (2015), Azar and Hage (2017), Toscanini et al. (2021)
Antibody detection	40–80%	78–95%	65–100%	58–75%	Hage et al. (2015), Azar and Hage (2017), Toscanini et al. (2021)
Antigen detection	43–83%	30–39%	25–88%	90–98%	Hage et al. (2015), Azar and Hage (2017), Caceres et al. (2018), Toscanini et al. (2021)
Molecular method	50%	-	-	95%	Hage et al. (2015), Azar and Hage (2017), Toscanini et al. (2021)
Pathology	0–42%	42%	75%	76%	Hage et al. (2015), Azar and Hage (2017), Toscanini et al. (2021)

3.5 Evaluation for dissemination

Since skin and mucosal lesions are signs of dissemination, patients with skin and mucosal lesions should be evaluated for dissemination. Appropriate testing should include ultrasound or computerized tomography (CT) abdomen for hepatosplenomegaly and adrenal enlargement, upper and lower gastrointestinal endoscopy for intestinal lesions, echocardiogram for endocarditis (rare) and bone marrow biopsy if pancytopenia is present. Other rare sites of disease include meningitis (antigen testing of CSF), larynx (biopsy, histopathology, culture, and antibody) and the mediastinum (fibrosing mediastinitis, with characteristic radiology).

Blood, respiratory samples, and bone marrow samples for fungal cultures could be sent to a fungal diagnostic laboratory if disseminated histoplasmosis is to be excluded. The yield of each culture specimen varies, with higher yields in disseminated histoplasmosis. In patients with HIV/AIDS who have disseminated histoplasmosis culture, the positivity rate of respiratory and blood samples may be up to 90% and 50%, respectively (Azar and Hage 2017). However, another study indicated that the sensitivity of blood culture was low as 36.6% among HIV patients with histoplasmosis (Medina et al. 2020). In Sri Lanka, a detailed evaluation of the patients for dissemination was only done in a few cases. Investigations of fungal culture of blood and bone marrow were not popular (only in cases 2 and 9) and on both occasions, they gave negative results (Harten et al. 1994, Jayathilake et al. 2020). Adrenal function tests were evaluated in only two patients with disseminated histoplasmosis, and one was abnormal. Radiological evaluation with abdominal ultrasound was done in three cases and revealed hepatosplenomegaly (Harten et al. 1994, Dhammika et al. 2017, Jayathilake et al. 2020), adrenal mass (Jayathilake et al. 2020) adrenal calcification (Harten et al. 1994), and para-aortic lymphadenopathy (Jayathilake et al. 2020). Two out of four endoscopic procedures showed changes; case 3 had whitish erosions in the esophagus (Karunanayaka et al. 2009) and colonoscopy in patient 5 showed severely inflamed mucous membrane of the colon (Dhammika et al. 2017) along with scattered aphthoid ulcers suggestive of dissemination.

3.6 Evaluation for immunodeficiency

Histoplasmosis, especially in its disseminated form, can represent immunodeficiency or underlying comorbidities. Three patients in the selected studies were previously healthy without known comorbidities (Harten et al. 1994, Dhammika et al. 2017, Keragala et al. 2020). The most frequently observed comorbidity among the patients was diabetes mellitus (Vidanagama et al. 2010, Jayawardena et al. 2019, Jayathilake et al.

2020, Sigera et al. 2020). In addition, one patient presented with non-Hodgkin lymphoma (Karunanayaka et al. 2009) and another with Chronic Obstructive Pulmonary Disease (COPD) (Sigera et al. 2020). Six of the patients were investigated for HIV status, all were negative. Immunological investigations other than HIV were conducted only in two cases (Harten et al. 1994, Keragala et al. 2020) and tests were normal.

Histoplasmosis is closely associated with immunological defects (Table 5) and might be the first sign of the presence of immunodeficiency (Scully and Baddley 2018). Patients with disseminated histoplasmosis should be evaluated for either primary or secondary immunodeficiency (Diwakar et al. 2015).

Table 5. Immunodeficiency associated with histoplasmosis

Primary immunodeficiency	**Secondary immunodeficiency**
IFN-γ/IL-12axis issues	Advanced HIV disease
STAT1 GOF mutations	Solid Organ transplantation
AD GATA2 deficiency	Stem cell transplantation
AR-DOCK8 deficiency,	Haematological malignancy
Idiopathic CD4 lymphopenia	Corticosteroid therapy
Common variable immunodeficiency (CVID)	TNF-alfa blockers or other immunosuppressive therapy
Hyper-IgE syndrome	Adult immunodeficiency syndrome (anti-gIFN antibodies)
X-linked hyper-IgM syndrome	

Histoplasmosis develops among 2–25% of HIV/AIDS patients in endemic regions (Limper et al. 2017). Although Sri Lanka's estimated prevalence of HIV is below 0.1%, a slow rise in the number of HIV cases has been observed over the last few decades, and 30% of patients possess advanced HIV infection (National STD/AIDS Programme, Ministry of Health, Sri Lanka 2020, UNAIDS 2021, Karunaratne et al. 2018). For example, a cumulative total of 1649 HIV patients were detected by 2012 after the first Sri Lankan with HIV infection was diagnosed in 1987 (National STD/AIDS Programme, Ministry of Health, Sri Lanka 2014). Sri Lanka has seen a cumulative total of 3,993 HIV patients and 1,381 deaths in HIV patients from 1987 to 2020 (National STD/AIDS Programme, Ministry of Health, Sri Lanka 2020). Moreover, 3,700 adults and children were living with HIV in Sri Lanka in 2020 (National STD/AIDS Programme, Ministry of Health, Sri Lanka 2020, UNAIDS, 2021). None have been diagnosed with histoplasmosis.

Chu et al. (2006) show in their population-based national study in the USA for endemic mycosis that 14% of histoplasmosis patients had an immunocompromising condition including solid organ transplantation. Like other countries, an increasing number of solid organ and bone marrow transplants are being done in Sri Lanka resulting in growth of the at-risk population (Abeysinghe et al. 2018, Vadysinghe et al. 2018, Gunetilleke et al. 2021). For example, four hundred kidney transplants were conducted in Sri Lanka in 2017 (Vadysinghe et al. 2018).

Immunomodulating treatments used in autoimmune conditions such as rheumatoid arthritis and inflammatory bowel disease pose a significant threat to acquire histoplasmosis (Scully and Baddley 2018). For example, the estimated average incidence of histoplasmosis among patients on infliximab was high as 18.8 per 100,000 patients (Wallis et al. 2005). Seventy-six percent of disseminated cases and a 3.2% of mortality rate were observed in a review of 98 cases of histoplasmosis associated with tumor necrosis factor therapy (Vergidis et al. 2015). Accordingly, histoplasmosis might be a future threat to the growing at-risk populations mentioned above in Sri Lanka and should be addressed accordingly.

3.7 Therapy

Antifungal treatment is recommended in severe or moderately severe acute pulmonary, chronic pulmonary, disseminated and CNS histoplasmosis. Amphotericin B, liposomal amphotericin B, amphotericin B lipid complex and itraconazole are the effective and preferred antifungals for the treatment of histoplasmosis (Wheat et al. 2007a). However, antifungal treatment of histoplasmosis poses a challenge to the physicians of low and middle-income countries because of the lack of sustainable supply of antifungals to those countries (Amona et al. 2021). The second factor is the high financial burden associated with the prolonged course of antifungals (Riera et al. 2019). In line with Infectious Diseases Society of America (IDSA 2007) guidelines, itraconazole and amphotericin B were the most frequently used antifungals to treat the patients of this review. Six patients were treated with itraconazole monotherapy (Karunanayaka et al. 2009, Vidanagama et al. 2010, Jayawardena et al. 2019, Jayathilake et al. 2020, Keragala et al. 2020, Prashanthi et al. 2021), and three patients were managed with IV amphotericin B followed by itraconazole (Harten et al. 1994, Dhammika et al. 2017, Sigera et al. 2020). Among these patients, most had favorable outcomes and only two patients died while on treatment. As seen in these cases, early diagnosis and treatment are mandatory for the successful outcome of the disease. However, outcome after long-term follow-up has been made only in selected cases. Table 6 shows the treatment and outcome of histoplasmosis patients reported in Sri Lanka.

Table 6. Treatment and outcome of patients reported in Sri Lanka

Drug	Clinical entity	Survival outcome
Itraconazole monotherapy	Chronic disseminated (SL case number 3, 6, 8, 9)	4/4 survived
	Localized (SL case number 4, 10)	1/2 survived
Amphotericin B followed by itraconazole	Acute disseminated (SL case number 2)	1/1 survived
	Chronic disseminated (SL case number 5)	1/1 survived
	Localized (SL case number 7)	1/1 death
Other	Localized (SL case number 1)	1/1 survived

4. Conclusions

Histoplasmosis has been reported from Sri Lanka for decades. The number of cases could be expected to be much higher than reported and is likely to rise further, along with the increase in at-risk populations. Oral lesions were the most observed clinical presentation of the patients and both betel chewing and diabetes mellitus are closely associated with oral lesions. Lack of awareness among medical professionals and inadequate laboratory facilities might have led to under-diagnosis of the condition. *Aspergillus* antigen testing could be a surrogate and rapid means of diagnosing acute disseminated histoplasmosis. It is essential to increase awareness among medical professionals and to enhance laboratory diagnostic facilities on histoplasmosis.

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