

## Histoplasmosis: A Neglected Tropical Disease in Humans Mimicking as Cancer

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### Abstract

Histoplasmosis is a kind of fungal infection usually developed in immunocompromised individuals. Initially, the causal organism, *Histoplasma capsulatum*, infects the lungs, developing pulmonary histoplasmosis. If not treated well within time, the disease may spread into other parts of the body as well. The disease may progress to either disseminated or chronic forms involving internal organs like adrenal glands, liver, spleen, lymph nodes, bone marrow, skin and mucous membranes, and the brain. The real paradox of the disease is that, in most of the cases, the disease is still being misdiagnosed as tuberculosis globally due to the radiological resemblances and the limited availability of rapid diagnostic tools. The physicians are unaware of the disease as it is not very much familiar amongst them. The present paper deals with the study of histoplasmosis, its epidemiology, discovery, clinical symptoms, oral manifestations, diagnosis, histopathology, methotrexate therapy and the development of facial/cutaneous histoplasmosis, and the histoplasmosis masquerading as cancer in the light of recent researches done so far in the field of emergency medicine and critical care.

**Keywords:** Histoplasmosis; *Histoplasma capsulatum*; Pulmonary and Disseminated Histoplasmosis; Oral Manifestations; Methotrexate; Histoplasmosis and Cancer

### Abbreviations

HIV: Human Immunodeficiency Virus; CD4: Cluster of Differentiation 4; WHO: World Health Organization; PAS: Periodic Acid-Schiff Reagent; TNF: Tumor Necrosis Factor; AIDS: Acquired Immunodeficiency Syndrome; POHS: Presumed Ocular Histoplasmosis Syndrome

### Introduction

Histoplasmosis is a granulomatous fungal infection developed by the *Histoplasma capsulatum*. The same fungus is usually found in soil rich in excreta of birds and bats. Birds and bat excrement enhance the growth of *Histoplasma capsulatum* in soil by accelerating sporulation. Sometimes, the sites that appeared quite free from contamination might also harbor the organism, making it very difficult to suspect developing histoplasmosis in humans. *Histoplasma* spores are released in air when contaminated soil is disturbed. Therefore, either the activities disturbing the site or the air currents carrying the spores may cause the disease [1] (Figure 1).

The disease is often developed in immunocompromised individuals, especially the patients with HIV/AIDS. Thus, the oral manifestation in HIV/AIDS patients should be examined cautiously, if suspected. Histoplasmosis is an opportunistic infection in immunocompetent as well as immunocompromised individuals by the inhalation of spores. However, it mainly occurs in individuals who are immunosuppressed with a CD4 count < 75 cells/ $\mu$ L [2,3].

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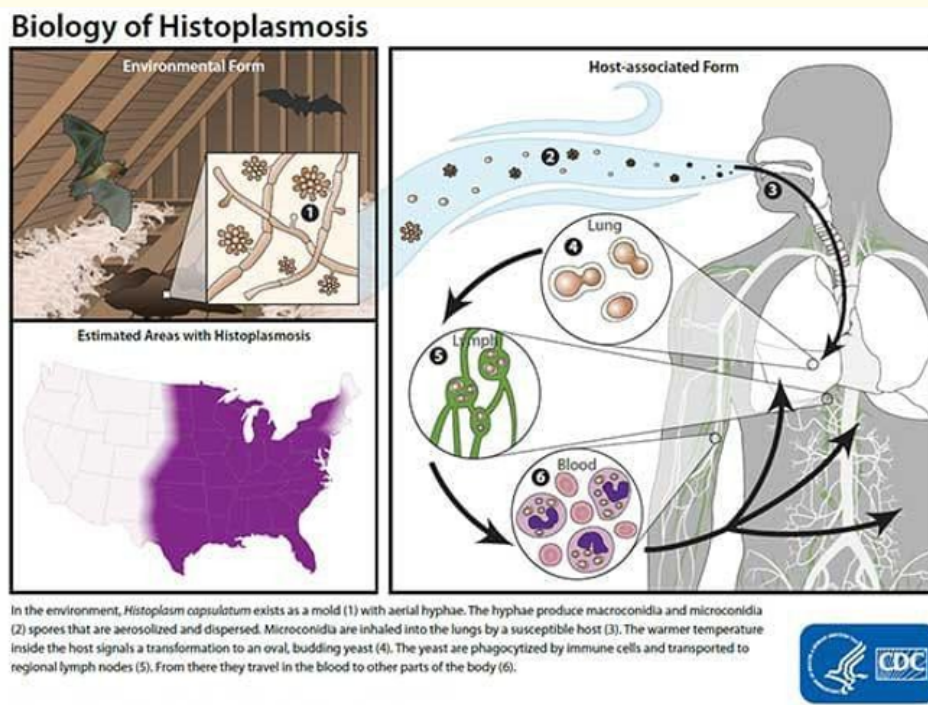


**Figure 1:** Biology of histoplasmosis infection in humans (Photo credited from CDC).

World Health Organization (WHO) has classified histoplasmosis in the category of neglected tropical diseases with “mycetoma”, chromoblastomycosis and other deep mycoses, recognizing it as an HIV/AIDS-defining opportunistic infection [4].

Mainly, there are three types of histoplasmosis found in humans. They are pulmonary, progressive disseminated and chronic cavitary forms. Initially, on exposure to the fungus, the infection is restricted to the lungs in 99% of individuals, while the remaining 1% progress to either disseminated or chronic forms involving other internal organs. Though, the cutaneous histoplasmosis is rare even in immunocompromised individuals, this is divided into primary and secondary lesions [3-7].

Further, the disease is often misdiagnosed as tuberculosis, particularly in immunocompromised individuals kept under immunosuppression, causing significant morbidity and mortality in resource-limited settings. Simultaneously, it has also been observed that over the past three decades, immunosuppressive therapies have become very popular without considering the hazards concerned with them, developing a variety of opportunistic infections including histoplasmosis in humans [8].

Therefore, the present paper highlights the need for increased awareness, diagnostic capabilities, identifying the knowledge gaps and the treatment modalities of histoplasmosis in the light of recent researches done so far in the field of fungal infections in medical microbiology.

### Epidemiology of the disease

Histoplasmosis is a fungal disease caused by the *Histoplasma capsulatum*. This is an endemic mycosis worldwide. The disease is reported in certain areas of eastern Asia, Australia, Africa, North, Central and South America, but the cases have also been reported

from Europe. Histoplasmosis is very common in Latin and North America. The disease is endemic in Ohio, Missouri and Mississippi river valleys. Similarly, several cases have been reported from Spain, France and Italy. Histoplasmosis in Australia is predominantly found in Queensland and New South Wales [9].

The advent of HIV pandemic has highlighted the epidemiology of histoplasmosis. However, the incidence of symptomatic histoplasmosis in Central and South America is not known, as many cases are misdiagnosed as tuberculosis. In some countries like French Guiana and Columbia, histoplasmosis is the most AIDS-defining illness [10].

Asia has also emerged as a region with a growing number of cases, particularly in India, China and Japan. In China, 75% of the reported cases are found within the basin of Yangtze River [10]. Southeast Asia is a hyperendemic area, with a prevalence of up to 33% [11].

Several cases have also occurred in Thailand, Malaysia, Indonesia, Singapore, Myanmar, Philippines and Vietnam. Further, the reported prevalence of histoplasmosis in Africa varies according to regions [12].

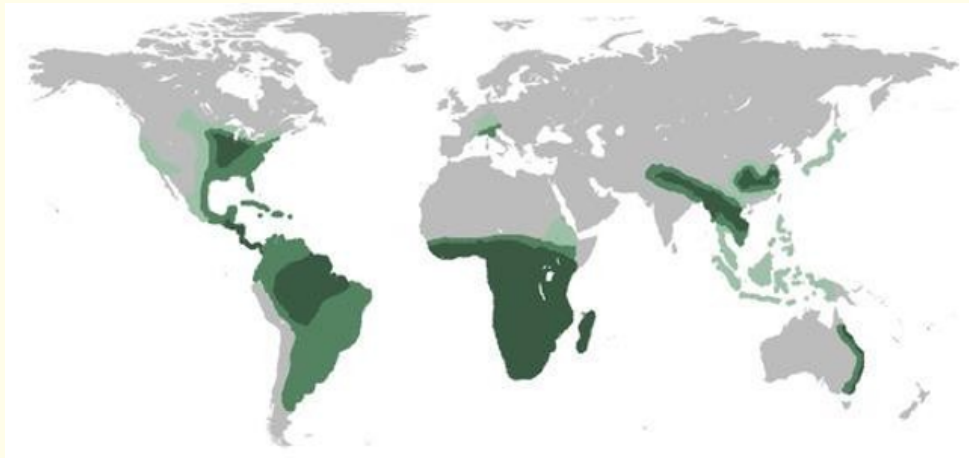


**Figure 2:** World map epidemiology of histoplasmosis where dark green, green and light green areas represent hyperendemic, infection occurs regularly and the areas of local infections respectively (Photo credited from Barros., et al. 2023) [10].

### Histoplasmosis in India

The first case of histoplasmosis was reported in India in 1959. Later on, it was observed that West Bengal is a prevalently affected state with 2 to 5% in acquired AIDS patients, while <0.05% in non-HIV patients [13].

The disease is considered endemic to the Gangetic plains, such as West Bengal and Uttar Pradesh. However, the reports from non-endemic regions have also been increasing. This is more frequently detected in advanced disseminated stage rather than at an early acute pulmonary stage. This might be due to the lack of awareness and radiological resemblances to infections like tuberculosis and the limited availability of rapid diagnostic tools. Similarly, since the nodules often resemble lung cancer on imaging, the patients must undergo unnecessary, costly and invasive procedures. Gastrointestinal histoplasmosis is very rare in India. Adrenal involvement has been reported in 30 to 40% of cases. Most of them were suffering from diabetes and presented with adrenal insufficiency [14,15].

### Discovery of the disease

Samuel Taylor Darling, an American pathologist and bacteriologist, discovered the pathogen *Histoplasma capsulatum* in Panama in 1905. He serendipitously investigated a dimorphic fungus while trying to understand malaria. He named it later as *Histoplasma capsulatum*, causing histoplasmosis or Darling's disease in humans [16-18].

### Etiology of the disease

*Histoplasma capsulatum* is the etiological agent of histoplasmosis in humans. It is a dimorphic fungus that grows as a mold in the environment and as a yeast in the human body. The disease is caused by two distinct microorganisms, such as *Histoplasma capsulatum* var. *capsulatum* and *Histoplasma capsulatum* var. *duboisii*. While *H. capsulatum* var. *capsulatum* is found on all continents except Antarctica, *H. capsulatum* var. *duboisii* is only found exclusively in Africa [9] (Figure 3 and 4).

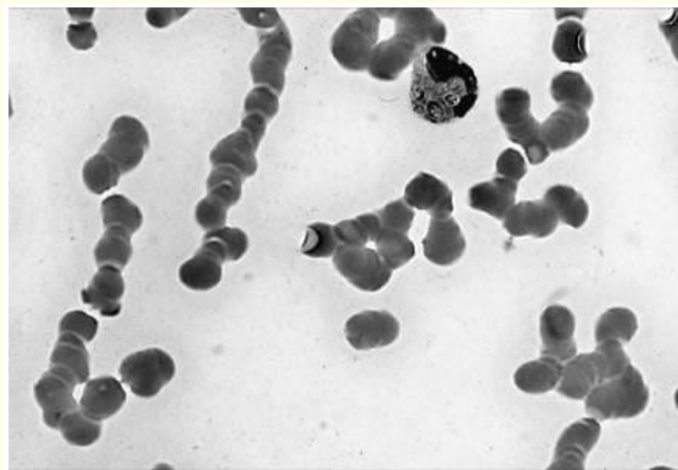


**Figure 3:** Yeast forms of *Histoplasma capsulatum* found in a neutrophil on a peripheral blood smear  
(Photo adapted from Kauffman 2007) [19].

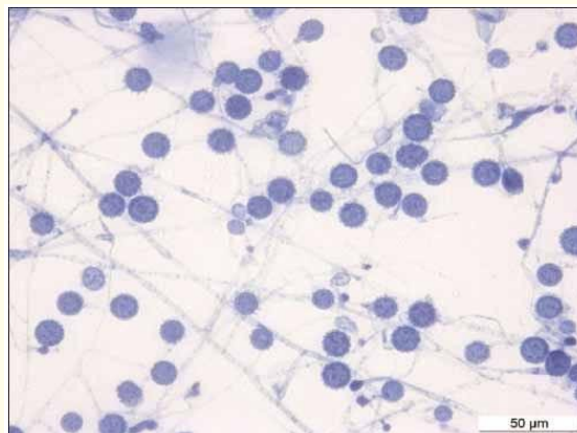


**Figure 4:** Hyaline and septate hyphae with numerous thick-walled and tuberculated macroconidia of *Histoplasma capsulatum* (Photo adapted from Brazo-Silva, et al. 2013) [20].

### Clinical symptoms and diagnosis of the disease

Since histoplasmosis is primarily a lung infection, its symptoms are almost similar to other pneumonias. The symptoms appear between 3 to 17 days after inhaling sufficient inoculum of fungal spores. The signs of histoplasmosis are headache, fever, cough, chills, fatigue, extreme tiredness, body ache and chest pain (Figure 5). The symptoms may be mild to severe. Severe infections may spread to other parts of the body as well, including the brain, to cause meningitis [6,19].

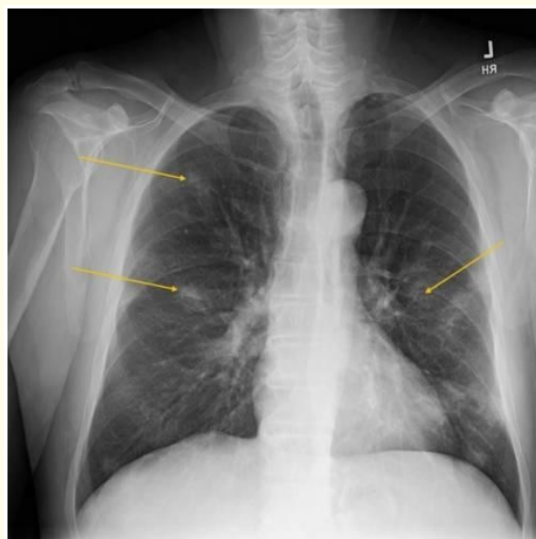


**Figure 5:** Chest X-ray of pulmonary histoplasmosis showing multiple hazy opacities

(Photo adapted from Khan., et al. 2020) [26].

Similarly, Presumed Ocular Histoplasmosis Syndrome (POHS) is a long-term complication developing vision loss due to choroidal neovascularization. Small white spots appear deep inside the eyes, called as “histo spots”. Diagnosis is based on histoplasmin skin test which is positive soon after exposure and remains positive throughout life. The disease was first reported in 1959 by Woods and Wahlen. The patients are being treated with the help of intravitreal ranibizumab (Lucentis®, Novartis) injections (Figure 6 and 7) [21-23].

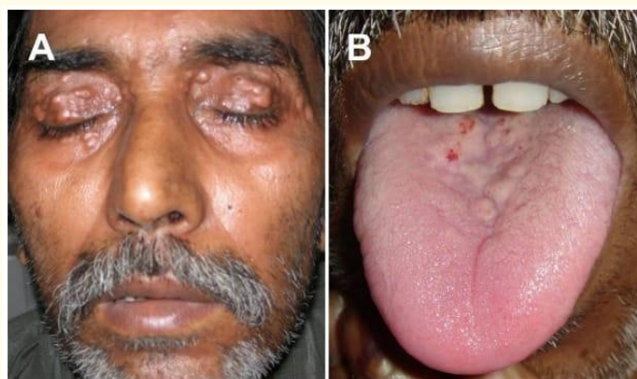


**Figure 6:** Facial dome-shaped umbilical papules of histoplasmosis on eyelids, glabella and eyebrows,

and tongue (Photo adapted from Sinha., et al. 2013) [27].



**Figure 7:** Small discrete mid-peripheral chorioretinal scars with macular choroidal neovascularization caused by ocular histoplasmosis in the left eye (Photo adapted from Yilmaz, et al. 2017) [22].

The disease is often diagnosed late because clinicians are not very much familiar with the disease. In India, this is increasingly recognized in patients with either adrenal involvement or disseminated disease and is often misdiagnosed as tuberculosis due to overlapping clinical features [15,24]. Similarly, in African countries, most of them are misdiagnosed as pulmonary tuberculosis. Moreover, disseminated cutaneous lesions are misdiagnosed as cryptococcosis or molluscum contagiosum [12] (Figure 4).

Further, despite its growing incidence, the disease is underdiagnosed due to lack of clinical awareness and diagnostic tools and resources. The availability of rapid diagnostic tools such as antigen detection is required for the early detection of the disease in patients. In a nutshell, it appears that there is still a need to acquire awareness amongst the health professionals of histoplasmosis to consider the correct diagnosis [25].

### Oral manifestations of histoplasmosis

Oral lesions of histoplasmosis are very rare. However, this is sometimes signaling either disseminated disease or underlying immunodeficiency like AIDS. These lesions are painful ulcerations with vegetative growths in the form of granulomatous nodules, frequently found on tongue, palate and gingiva. They are often misdiagnosed as squamous cell carcinoma. Oral histoplasmosis might be treated as an early indicator of AIDS [27-30] (Figures 8 to 10).

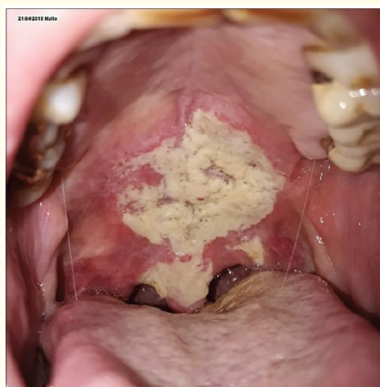


**Figure 8:** Oral manifestation of histoplasmosis with white carcinomatous plaque on soft palate approaching uvula (Photo adapted from Kondo, et al. 2021) [31].



**Figure 9:** Ulcerative fungative lesions of gingival and lingual histoplasmosis (Photo adapted from Folk and Nelson 2017) [28].



**Figure 10:** Multiple, deep, well-demarcated clear-based ulcers on dorsal and lateral side of the tongue caused by oral histoplasmosis (Photo credited from Hendren., et al. 2017) [32].

### Differential diagnosis and risk factors of the disease

Some of the differential diagnosis of pulmonary histoplasmosis are blastomycosis, coccidioidomycosis, valley fever, *Mycoplasma pneumoniae*, Chlamydial pneumonia, paracoccidioidomycosis, *Legionella* pneumonia, tuberculosis, non-tuberculous mycobacterial infection, sporotrichosis, aspiration pneumonitis and pneumonia, carcinoid lung tumors, fungal pneumonia, mediastinal cysts and lymphoma, Pancoast syndrome, pneumococcal infections and sarcoidosis. Similarly, some of the risk factors for disseminated histoplasmosis are age, hematological malignancies, solid organ transplant, immunosuppressive agents, AIDS, corticosteroids, congenital T-cell deficiencies, tumor necrosis factor antagonists, gamma interferon receptor deficiency and Hyperimmunoglobulin M syndrome [19,33].

### Histopathology of the disease

The fungus was detected by direct mycological examination with Grocott histopathological staining showing intracytoplasmic yeast structures. Fungal cultures are also performed to confirm the disease [3,15,20] (Figure 11 and 12).

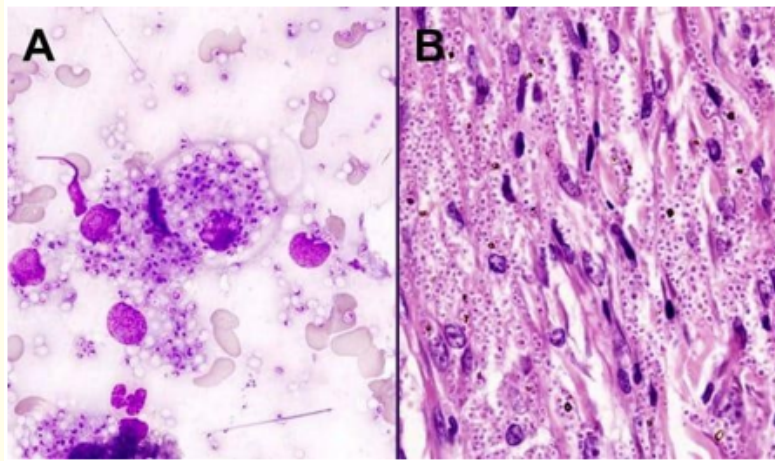


**Figure 11:** Fine needle aspiration cytology showing numerous intra- and extra-cellular tiny oval yeasts of *Histoplasma capsulatum* (A) and peripheral spaces with round to ovoid yeast cells (B) (Photo adapted from Sinha., et al. 2013) [27].

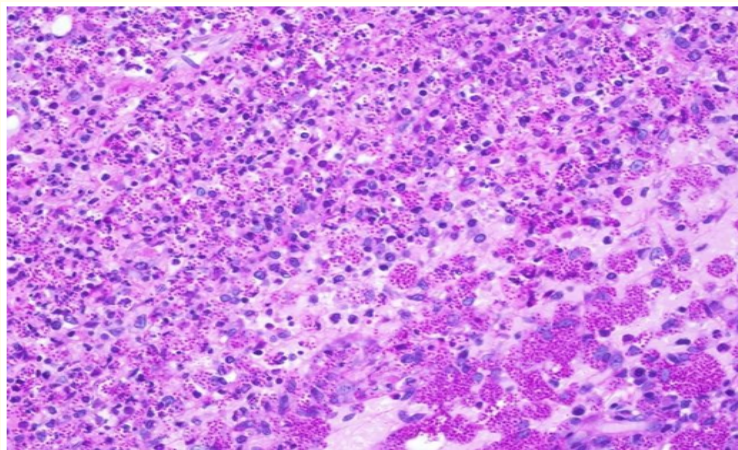


**Figure 12:** Visualization of yeast elements as *Histoplasma capsulatum* with Periodic acid-Schiff (PAS) reagent (Photo adapted from Folk and Nelson 2017) [28].

### Methotrexate and steroid therapy developed cutaneous facial histoplasmosis in immunocompromised individuals

Methotrexate, a medicine generally used to treat arthritis, even in a very low dose if prescribed for a longer period of time with steroids, especially in immunocompromised individuals, may cause cutaneous histoplasmosis. These individuals are at heightened risk of opportunistic infections including cutaneous facial histoplasmosis. Methotrexate itself is an immunosuppressive medicine used to treat arthritis, psoriasis, Crohn's disease and cancer by slowing down the immune system, reducing inflammation [34].

Immunosuppression from long-term methotrexate and corticosteroid therapy can cause reactivation or progressive disseminated cutaneous histoplasmosis on the face with ulcerated, crusted or nodular eruptions [35,36] (Figure 13 and 14).



**Figure 13:** A case of disseminated multiple cutaneous facial histoplasmosis in an immunocompromised female individual treated for arthritis with low doses of methotrexate and intermittent steroids (Photo adapted from Panuganti., et al. 2022) [35].



**Figure 14:** Cutaneous multiple skin-coloured erythematous papules, plaques and nodules on the entire face (Photo adapted from Vasudevan., et al. 2010) [13].

### Histoplasmosis masquerading as cancer

Histoplasmosis and cancer often intersect, each other mimicking primary lung tumors or metastases on imaging scans. Radiomics have potential utility in the challenging task of distinguishing between histoplasmosis and lung cancer [37,38]. Cancer patients kept under immunosuppression are at heightened risk for severe disseminated histoplasmosis. It leads to a misdiagnosis of benign fungal growths as primary lung cancer or metastasis, leading to unnecessary biopsies or surgeries [39].

Several triggering factors like chemotherapy, radiation, the use of corticosteroids, hematopoietic stem cell transplants and TNF-alpha antagonist therapies enhance the growth of fungal infections in cancer patients, including histoplasmosis [38]. Similar is the case with blood cancers like hairy cell leukemia and chronic lymphocytic leukemia [26,39].

### Histoplasmosis and lung cancer

Recent references often highlighted the crucial relationship between histoplasmosis with cancers such as lung cancer or lymphomas on scans. As histoplasmosis causes granulomatous lesions, pulmonary nodules and masses often mimic non-small cell lung cancer, tumors or metastases. Advanced diagnostic imaging techniques can only differentiate these benign histoplasmosis lesions from true malignancies without invasive biopsies [37,40].

### Histoplasmosis masquerading as head, neck and mucosal oral cancers

Oral and oropharyngeal histoplasmosis lesions are also frequently misdiagnosed as squamous cell carcinoma. It can lead to unnecessary catastrophic surgeries. A high degree of suspicion is needed to identify the fungus via biopsies [41,42].

### Histoplasmosis mimicry with multiorgans cancer

Histoplasmosis can masquerade with cancers involving adrenal glands, liver and spinal cord [39,43-45].

Finally, besides mimicking malignancies, histoplasmosis has been implicated in the development of cancers. Therefore, an area of research is required as a matter of urgency to mitigate the burden of cancers in future [38,39,45].

### Treatment of the disease

Amphotericin B and azole therapy have been the best choice of drugs for physicians. Itraconazole is mostly preferred. Lipid formulation of Amphotericin B followed by itraconazole is usually recommended (Amphotericin B: 3.0 - 5.0 mg/kg daily intravenously for 1 - 2 weeks followed by itraconazole: 200 mg 3 times daily for 3 days and then 200 mg twice daily for a total of 12 weeks). However, the length of treatment depends on severity of the disease [1,19].

Histoplasmosis developed due to methotrexate are being treated with intravenous amphotericin B and oral itraconazole antifungal therapy as the choice of drugs for physicians [6]. However, the patients who are unable to absorb itraconazole due to intractable diarrhoea were subsequently treated with isavuconazole and steroids with full recovery. This is a newer antifungal drug with more potential and a better safety profile. The drug is available in oral as well as intravenous forms [46].

### Conclusion

The present paper discusses a kind of fungal pulmonary infection as histoplasmosis in humans. The disease was first highlighted by Samuel Taylor Darling in 1905 from Panama. Histoplasmosis has already been reported from eastern Asia, Australia, Africa, America and in certain parts of Europe. The disease was reported from India in 1959. This is generally endemic to the Gangetic plains such as West Bengal and Uttar Pradesh.

The disease is most commonly found in either immunocompromised individuals or in individuals kept under immunosuppression; however, it has also been commonly found in immunocompetent individuals. Since histoplasmosis is primarily a lung infection, its symptoms are similar to pneumonia. The incubation period is 3 to 17 days depending on the quantity of inoculum inhaled. The first signs of histoplasmosis are headache, cough and fever, chills, fatigue, extreme tiredness, body ache and chest pain. If not treated well within time, infections may spread to other parts of the body as well. Though oral manifestations are rare, they sometimes signal either disseminated disease or underlying immunodeficiency like AIDS. Oral manifestations might be treated as an early indicator of AIDS. These ulcerative and painful oral lesions are often misdiagnosed as squamous cell carcinoma.

The present paper also discusses histoplasmosis as a most neglected tropical disease which is not very much familiar amongst physicians. That is why the disease is often misdiagnosed as tuberculosis. This might be due to the radiological resemblances with tuberculosis, lack of knowledge and the limited availability of rapid diagnostic tools. Similarly, sometimes the disease is also masquerading as cancer, leading to a misdiagnosis of benign fungal growths as primary lung cancer or metastasis involving unnecessary biopsies or surgeries. Pulmonary histoplasmosis also produces granulomatous pulmonary nodules and masses, often mimicking non-small cell lung cancer, tumors or metastases. Unfortunately, only advanced technologies can differentiate the lesions without invasive biopsies. The paper also described a case study involving the use of methotrexate and steroids for the treatment of arthritis patients with an outcome of cutaneous facial histoplasmosis. Last, but not the least, histoplasmosis has successfully been treated with amphotericin B and azole therapy.

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### Conflict of Interest

The authors have declared no conflicts of interest. Compliance with ethical standards: The article does not contain any studies involving either human or animal subjects.

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### Ethical Clearance

Since the article is purely a review work, hence it does not require an Ethical Clearance.

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