



## Disseminated Histoplasmosis in an Immunocompetent Patient from a Non Endemic Region, North India: Pointers to Potential Endemicity

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### Authors' contributions

This work was carried out in collaboration between all authors. Authors AK and DB identified the isolate, wrote the first draft of the manuscript and edited the final version. Author SR performed the radiological work up of the patient and edited the manuscript. Author NS did the histopathological identification. Author BK did literature search and edited the manuscript. All authors read and approved the final manuscript.

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Case Study

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### ABSTRACT

Progressive Disseminated Histoplasmosis (PDH) reported worldwide is yet a rare entity in India. Although, usually associated with an underlying immunocompromised state but few reports of this disease in non-immunocompetent individuals have been surfacing in last decade. We report PDH from Himalayan state of Uttarakhand North India in an agriculturist, non immunocompromised who

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responded well to treatment with no evidence of recurrence of the disease. Of late a number of cases are being reported from this region, an indication that this might be a hot spot of *Histoplasma capsulatum*.

**Keywords:** *Progressive disseminated histoplasmosis; immunocompetent; Histoplasma capsulatum var capsulatum; amphotericin; antifungal resistance.*

## 1. INTRODUCTION

*Histoplasma capsulatum* is caused by a dimorphic fungus *Histoplasma capsulatum* [1]. Clinical presentation ranges from asymptomatic or mild, self-limiting infections in immunocompetent patients to severe disseminated infection in the immune-compromised. Persons exposed to soil and contaminated water supplies are particularly at risk of developing pulmonary histoplasmosis. This disease is endemic particularly in the Ohio and Mississippi river valleys of North America. However, the disease is being reported frequently from non-endemic areas especially among immune compromised individuals. In India, Panja and Sen reported the first case of histoplasmosis from Calcutta [2]. This was followed by several reports of histoplasmosis in residents of Bengal, sporadic reports from Maharashtra and other parts of the country [3,4]. The diagnosis is mainly done by direct microscopy, culture of *H. capsulatum* from clinical samples, conversion to yeast form, characteristic microscopic appearance. Molecular studies may sometimes be needed in order to clinch the diagnosis. We report here a case of disseminated histoplasmosis in an immunocompetent patient from Himalayan state of Uttarakhand in North India, which has till date not been known to be an endemic focus of this disease.

## 2. CASE HISTORY

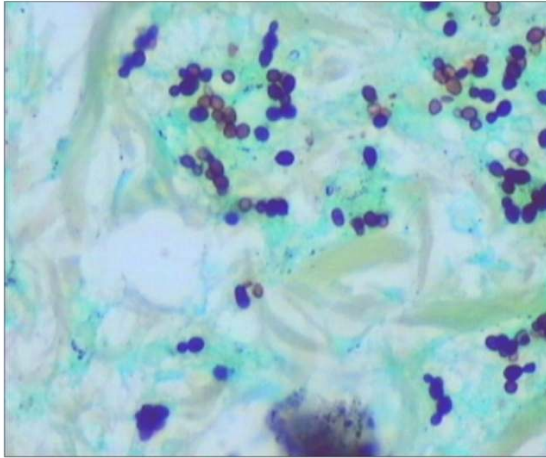
A 60 year - old gentleman, agricultural worker by profession, presented to us with history of irregular episodes of fever for the last 3 months, and generalized weakness and weight loss for 1 year. The patient had been admitted to various hospitals within the last one year and had undergone extensive diagnostic workup. Upon arrival at our hospital, the patient was found to have fever (temperature 103°F at admission) with chills, along with severe fatigue. On examination, bilateral axillary lymphadenopathy and disseminated cutaneous dermal nodules were observed. He had no relevant co-morbid condition and denied any history of travel outside

the state of Uttarakhand. Routine hematological work-up was unremarkable, except for the presence of moderate anemia (Hemoglobin= 8.69 g/dL), lymphopenia (5%) and markedly raised ESR (erythrocyte sedimentation rate) (80 mm/hr). Peripheral blood smear revealed microcytic hypochromic anaemia with occasional polychromatic cells. His biochemical parameters, including hepatic and renal function tests and electrolytes, were normal. His HIV status was negative with CD4 counts being well above normal (1400 cells/ $\mu$ l) and he had no history of being on cytotoxic drugs or corticosteroids. Blood cultures and urine culture remained negative. Ultrasound of the abdomen revealed mild hepatosplenomegaly but patient refused liver biopsy. There was no enlargement of intraabdominal nodes. Chest X- ray was also normal but high resolution CT (computed tomography) scan of the chest revealed features of diffuse reticulonodular shadows. Fine needle aspiration cytology from an enlarged axillary lymph node revealed population of mostly monomorphic cells with features suggestive of Non-Hodgkins lymphoma. However, a bone marrow examination revealed no malignant cells suggestive of any haematological malignancy but showed abundant ill-defined granulomas with yeast cells (Fig. 1a). Bone marrow aspirate was inoculated in Brain heart infusion broth and incubated in parallel at 37°C and 25°C. Skin biopsy was done from the dermal nodules which were consistent with deep dermal fungal infection (the microphotographs not included due to poor quality of images). Skin tissue was inoculated on Sabouraud's dextrose agar at 37°C and 25°C for microbiological confirmation of fungal etiology.

After 3 weeks of incubation at 37°C, yeast-like colonies were grown that were rough, cream colored on obverse and non pigmented on reverse (Fig. 1b). At 25°C, flat buff-colored growth was observed that were heaped towards the center and brown colored on the reverse. LCB (Lactophenol cotton blue) staining from growth obtained at 25°C showed large tuberculate globose macroconidia and round 6-15  $\mu$  microconidia borne on short lateral hyphae (Fig. 1c). An LCB mount from growth at 37°C

demonstrated oval yeast cells with narrow base budding. These findings were suggestive of *Histoplasma capsulatum*. The isolates were sent to the referral center at National Culture Collection of Pathogenic Fungi, Post Graduate Institute of Medical Education and research, Chandigarh, India, where the isolate was confirmed to be *Histoplasma capsulatum var capsulatum*.

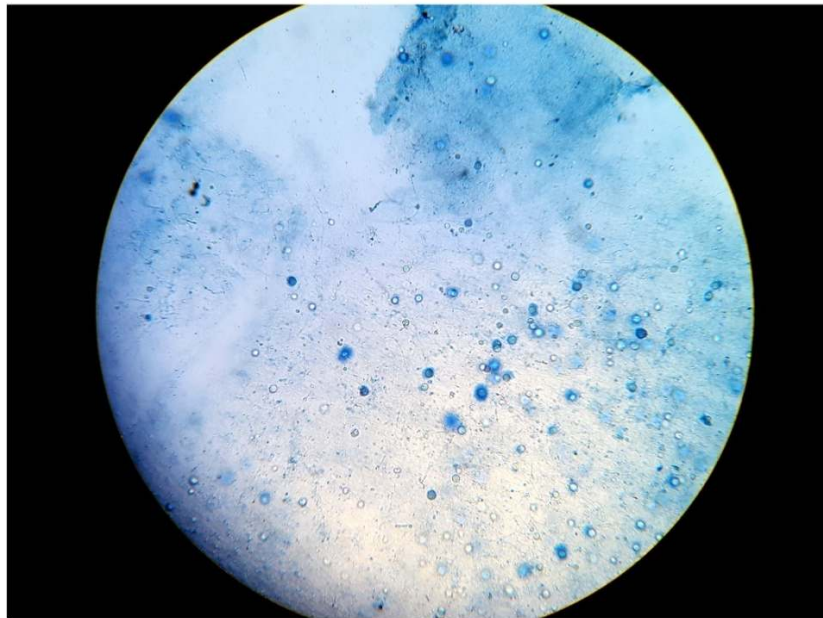
Patient was started on liposomal amphotericin B (3.0 mg/kg daily) for 2 weeks, followed by oral itraconazole (200 mg three times daily for 3 days and then 200 mg twice daily). He responded well to treatment with no adverse effects and has shown no recurrence of disease in course of the last six months of follow-up.



**Fig 1(a).** Hematoxylin and eosin(H&E Stain)(100X) staining showing *Histoplasma capsulatum*.



**Fig 1(b).** Buff brown colonies of *Histoplasma capsulatum* on Sabouraud's dextrose agar at 25°C, after 1 week of incubation



**Fig 1(c).** Lactophenol cotton blue mount (400X) showing large, rounded, single-celled, tuberculate macroconidia(Black arrow) and small, pyriform shaped microconidia(Blue arrow) of *Histoplasma capsulatum*.

### 3. DISCUSSION

In this paper, we report the occurrence of Progressive Disseminated Histoplasmosis in an apparently healthy and immunocompetent person, from a non-endemic location in the Himalayan region of North India.

Our case had several unique characteristics. Epidemiologically, Histoplasmosis is known to be commonest endemic fungal infection in humans with the regions of endemicity spanning over the central river valleys in Midwestern and south central United States. Over 80% of young adults from the Ohio and Mississippi river valleys have been demonstrated to be infected with *H. capsulatum* [5]. River valleys between latitudes 45°N and 30°S in South and Central America are also known to be endemic for this fungus [6]. However, despite the presence of extensive river basins across the Indian landscape, reports of Histoplasmosis from India have always been scattered in distribution and relatively few in number. Probably, the hot and humid tropical climate across the riverine plainlands in India preclude the endemic occurrence of this disease. The present case hailed from the Himalayan state of Uttarakhand and contrary to the geographical context in major stretches of India, this state presents a cool, mountainous semi-tropical climate for large parts of the year and is also the source of all of the major rivers of North India. We believe that reporting of this index case from this epidemiological background would raise diagnostic suspicion for Histoplasmosis in cases of undiagnosed fever or unexplained pulmonary lesions and could lead to the potential identification of newer foci of endemicity for this fungus.

The clinical presentation of this case was relatively unusual in being devoid of any apparent immunocompromising risk factor. Disseminated Histoplasmosis is characteristically associated with infants, AIDS patients with CD4 counts below 150 cells/ $\mu$ l, use of corticosteroids, hematological malignancy, solid organ transplantation, use of TNF $\alpha$  antagonists, etc [7,8]. Though none of these risk factors were present in this patient, it is possible that repeated occupational exposure in course of his agricultural work could have led to the chronic exposure to fungal conidia and mycelia fragments. Acidic, damp soil with high organic content, near areas inhabited by birds and bats, is known to provide enriching conditions for the growth of *Histoplasma* [9,10]. This further

strengthens our suspicion for a potential zone of endemicity in Uttarakhand, in view of the commonness of agricultural profession and manual agricultural practices in this state. We intend to undertake sero-epidemiological studies in the state among healthy individuals and undiagnosed febrile patients, in our bid to explore the potential endemicity for Histoplasmosis in Uttarakhand.

### 4. CONCLUSION

This report underscores the importance of maintaining suspicion for Progressive disseminated Histoplasmosis in patients who have features of this mycotic disease but live in a non-endemic area.

### CONSENT

All authors declare that written informed consent was obtained from the patient for publication of this paper and accompanying images.

### ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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