

## Short Report

### Disseminated histoplasmosis: A comparative study of the clinical features and outcome among immuno- compromised and immunocompetent patients

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#### ABSTRACT

**Background.** Disseminated histoplasmosis is a chronic granulomatous disease caused by the dimorphic fungus, *Histoplasma capsulatum*. Clinical presentation can vary from the acute pulmonary to the chronic disseminated form. In India, disseminated histoplasmosis often presents with pyrexia of unknown origin with a presentation similar to 'disseminated tuberculosis' involving the adrenal glands and bone marrow. Due to rarity of the disease, data are lacking regarding its clinical presentation and outcome among immunocompromised and immunocompetent patients.

**Methods.** During January 2000 to December 2010, we identified 37 patients of disseminated histoplasmosis and attempted to characterize the differences between immunocompromised and immunocompetent patients. Demographic characteristics, clinical presentation, risk factors, laboratory findings, diagnostic yield, treatment received and prognosis were noted and compared between the two groups.

**Results.** Eleven of 37 patients with disseminated histoplasmosis were immunocompromised and 26 were immunocompetent. Comparison of their clinical features showed a higher frequency of skin lesions in the immunocompromised compared to the immunocompetent group (54.5% v. 11.5%). Pancytopenia and anaemia were more common among the immunocompromised (81.8%) compared to the immunocompetent (46.2%) group. In the immunocompromised patients, the diagnosis was made most often by bone marrow aspirate and culture (72.7%) compared to the immunocompromised group where the diagnosis was most often obtained by adrenal gland biopsy and fungal cultures

(57.7%). The cure rate was significantly higher in the immunocompetent group (73% v. 45%).

**Conclusion.** The clinical presentation and outcome of patients with disseminated histoplasmosis differs among immunocompromised and immunocompetent patients.

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#### INTRODUCTION

Disseminated histoplasmosis (DH) is a progressive granulomatous disease caused by the dimorphic intracellular fungus, *Histoplasma capsulatum*. It was first described in 1906 by Samuel Taylor Darling in a patient who died of miliary tuberculosis.<sup>1</sup> Studies have shown isolation of *H. capsulatum* from the soil of West Bengal<sup>2</sup> and the first case of histoplasmosis was reported from India in 1954 by Panja and Sen<sup>3</sup> from Calcutta. A third of the cases in a series from northern India<sup>4</sup> and a series reported from our institution in southern India<sup>5</sup> have originated from West Bengal which has a hot and humid climate with high rainfall. A number of risk factors can predispose to DH such as AIDS, primary immunodeficiency, long-term immunosuppression as with use of glucocorticoids, post-organ transplantation and extremes of age.<sup>6,7</sup>

DH is a relatively rare disease which often presents as pyrexia of unknown origin. It can mimic tuberculosis and thus making a diagnosis can often be difficult. In our previous series we elaborated on the clinical features and natural history of DH.<sup>5</sup> In India, we note an unusual presentation of 'histoplasmosis' called Asian histoplasmosis which is distinct from what is observed elsewhere in the world.<sup>8</sup> As our experience with histoplasmosis increased, we observed a difference in clinical presentation among immunocompromised and immunocompetent patients. Hence, we studied these differences and present our findings here.

#### METHODS

Data were collected from the records of in-patients of all adult patients with DH who were admitted to Christian Medical College, Vellore (a tertiary care hospital) from January 2000 to December 2010. DH was diagnosed (based on definitions from our previous study) if (i) histology and tissue from extrapulmonary sites revealed granulomas and intracellular yeast-like organisms, or (ii) fungal culture of extrapulmonary tissues such as skin, mucosa, bone marrow, liver or spleen grew *H. capsulatum*. Patients' demographic profile, clinical presentation, treatment details and outcome were studied. Patients who had evidence of granulomas without the demonstration of fungal organisms on histopathology were excluded. Subsequently, they were categorized into immunocompetent and immunocompromised individuals. An immunocompromised individual was defined as a person who had a definite cause for immunocompromise: (i) co-infection with HIV; (ii) neutropenia (absolute neutrophil count <500 cells/cmm); or (iii) any other cause of congenital or acquired immunodeficiency. The rest of the patients formed the immunocompetent group. The data were analysed and differences in presentation and outcome were studied.

#### RESULTS

Of the 37 patients with DH, 11 were immunocompromised and 26

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TABLE I. Clinical features of disseminated histoplasmosis among immunocompromised and immunocompetent patients

Clinical feature	Immuno-compromised group n=11 (%)	Immuno-competent group n=26 (%)	p value
Fever	11 (100)	23 (88.5)	0.16
Weight loss	10 (90.9)	22 (84.6)	0.33
Oral ulceration	2 (18.2)	5 (19.2)	0.48
Skin lesions	6 (54.5)	3 (11.5)	<0.01
Gastrointestinal ulceration	3 (27.3)	3 (11.5)	0.14
Hyperpigmentation	1 (9.1)	1 (3.8)	0.29
Pallor	9 (81.8)	12 (46.2)	0.10
Lymphadenopathy	7 (63.3)	6 (23.1)	0.01
Hepatosplenomegaly	6 (54.6)	10 (38.5)	0.19

were immunocompetent. Among the 11 patients who were immunocompromised, 10 (90.9%) were men. The mean age in the immunocompromised group was 39.1 years and in the immunocompetent group it was 52.2 years.

The majority of patients in the immunocompromised (72.7%) and immunocompetent (61.5%) groups belonged to West Bengal. Fever, weight loss and oral ulcers were seen equally in both the groups. Skin lesions (54.5% v. 11.5%;  $p < 0.01$ ) and lymph node enlargement (63.3% v. 23.1%;  $p = 0.01$ ) were significantly higher in the immunocompromised compared to the immunocompetent group. Pallor and hepatosplenomegaly were also higher in the immunocompromised group (Table I).

Among the laboratory parameters, pancytopenia was seen in 9 of 11 (81%) among the immunocompromised group compared to 10 of 26 (38.4%) in the immunocompetent group. Liver involvement in the form of transaminitis and elevated alkaline phosphatase was seen equally in both groups. Imaging revealed that adrenal involvement was present in 1 of 11 (9%) among the immunocompromised compared to 13 of 26 (50%) among the immunocompetent group. Of the 14 patients who had adrenal involvement, 3 (19.2%) were adrenal insufficient as well.

The diagnosis of DH was made by bone marrow aspiration and fungal culture of the aspirate and biopsy in 8 of 11 (72.2%) immunocompromised compared to 14 of 26 (57.7%) immunocompetent patients in whom the diagnosis was obtained by adrenal gland biopsy and or fungal cultures.

All patients in the immunocompetent group and 7 of 9 patients in the immunocompromised group opted for treatment. More than two-thirds of the patients in both groups received conventional amphotericin B followed by itraconazole, while the others received itraconazole alone (Table II).

The cure rate was higher among the immunocompetent group (73.1%) compared to the immunocompromised group (45.5%). Seven patients died, 3 (27.3%) among the immunocompromised group and 4 (15.4%) among the immunocompetent group (Table II).

## DISCUSSION

We have, in a reasonably large group of patients with DH,

TABLE II. Treatment of disseminated histoplasmosis among immunocompromised and immunocompetent patients

Treatment	Immuno-compromised group n=11 (%)	Immuno-competent group n=26 (%)	p value
Treatment received	9 (81.8)	26 (100)	—
Amphotericin followed by itraconazole	8 (72.7)	16 (61.5)	0.28
Itraconazole alone	1 (9.1)	10 (38.5)	0.04
Cured	5 (45.5)	17 (65.4)	0.06
Persisted	2 (18.2)	2 (7.7)	0.21
Relapsed	1 (9.1)	1 (3.8)	0.28
Died	3 (27.3)	4 (15.4)	0.21

compared the differences in demographic profile, clinical presentation and outcome among immunocompromised and immunocompetent patients. Although fever and weight loss were the most common presenting complaints among both groups, similar to the previous study done in this institution,<sup>5</sup> we found that skin lesions such as nodules, papules and plaques were more common among the immunocompromised group. As has been shown in other studies,<sup>8,9</sup> we also noted that adrenal involvement occurred mainly among the immunocompetent compared to the immunocompromised and diagnosis in the former was obtained from biopsy and adrenal tissue fungal cultures. In contrast, among the immunocompromised group, bone marrow involvement was prominent and manifested as pancytopenia in most patients. Diagnosis in them was obtained by bone marrow biopsies and fungal cultures of the bone marrow aspirate.

The outcome of DH was better in the immunocompetent compared to the immunocompromised group.

To conclude, DH in an immunocompromised individual presented with a syndrome complex of prolonged fever, skin lesions and pancytopenia with a diagnosis most often made by a bone marrow biopsy and fungal cultures of the bone marrow aspirate. In immunocompetent patients DH often presented with prolonged fever and features of adrenal gland enlargement on imaging with diagnosis most often obtained by a fungal culture or adrenal gland biopsy.

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