Disseminated Histoplasmosis


Abstract

Objective: To study the clinical features and natural history of disseminated histoplasmosis (DH) in India.

Methods: We retrospectively analyzed the data obtained from the in-patient medical records of adults (age >13 years) diagnosed to have DH during the period from January 1989 to December 1999. DH was diagnosed when histologically compatible intracellular organisms were present or *Histoplasma capsulatum* was obtained in culture from the extrapulmonary sites.

Results: Nineteen patients (18 male and 1 female) were diagnosed to have DH. Diabetes mellitus and HIV infection were the most common co-morbid conditions. Weight loss, fever and oropharyngeal ulcers were the commonest symptoms. Physical signs included hepatosplenomegaly, oropharyngeal ulcers and lymphadenopathy. The diagnosis was confirmed by histopathology and/or culture from the following sites: bone marrow, adrenal gland, lymph node, oropharyngeal ulcers, rectal mucosa and skin. Two patients were treated with Amphotericin B, 6 with various azoles and 3 had Amphotericin B followed by various azoles. Among the eleven treated, 7 were cured, 2 improved, 1 had a relapse and 1 patient died.

Conclusion: DH is not uncommon in India and should be considered in the diagnosis of patients with prolonged fever, weight loss, oropharyngeal ulcers, hepatosplenomegaly, lymphadenopathy and adrenal enlargement. Correct diagnosis and treatment leads to a favourable outcome. ©

INTRODUCTION

Disseminated histoplasmosis (DH) is a relentlessly progressive granulomatous disease caused by the intracellular dimorphic fungus, *Histoplasma capsulatum*. Samuel Darling, in 1905, first identified this pathogen in the visceral tissues and bone marrow of an adult male presumed to have died of miliary tuberculosis.1 The organism exists in the mould (mycelial) form at soil temperatures and switches to the yeast form at normal human body temperatures (37°C) and resides within macrophages. The quality of the surface soil (upper 15 cm) that supports growth of organism is usually found in the vicinities of chicken houses, roosting places of birds and bat caves that abound in decaying guano. The mycelial form of *H. capsulatum* has two conidia - the macroconidia and the microconidia. The latter are smaller infective forms, which are 2-5 micrometer in diameter, and are oval and smooth. During outdoor activities such as spading of soil, deconstruction of chicken coops, spelunking etc., aerosolized microconidia are inhaled, settle in the alveoli and are then ingested by the alveolar macrophages. The microconidia convert to the yeast form and replicate within the macrophages, and then spread to the regional lymph nodes, and throughout the reticulo-endothelial system. The transition from the mycelial to the yeast form is heat sensitive and is crucial for the development of the infection. The infected macrophages induce cytokines in order to enlist more macrophages and monocytes to fight the organism, and these coalesce together to form granulomas. This activation of the T-cell mediated immune response is usually complete within two weeks and failure of this result in the progressive spread of infection to other organs.

Histoplasmosis may present clinically in different forms - asymptomatic infection; an acute or chronic pulmonary infection; mediastinal fibrosis or granulomas; and disseminated histoplasmosis. The development of progressive DH indicates impaired cell mediated immune responses. The acute form of DH is seen mostly in the immunocompromised host, and is characterized by an abrupt onset of symptoms (fever, malaise, hepatosplenomegaly, lymphadenopathy, anemia, leucopenia and thrombocytopenia), lack of granulomatous inflammatory response and high case-fatality rates. The chronic form of DH is characterized

*Lecturer; **Professor in the Department of General Medicine Unit 1 and #Professor of Clinical Microbiology, Christian Medical College, Ida Scudder Road, PB No. 3, Vellore, Tamil Nadu, India. Pin : 632004.
Received : 2.6.2004; Revised : 16.11.2004; Accepted : 2.12.2004
by an indolent course, focal lesions and an effective cell mediated immune response. The subacute DH pursues a subacute, but relentless course and focal lesions in various visceral organs.

In India, histoplasmosis seems to be prevalent in the Gangetic delta. Panja and Sen reported the first case of DH from Calcutta in 1954 and since then individual cases have been reported from various states, mostly from West Bengal. Among the forms of histoplasmosis reported from India, DH is the rarest. We have summarized here a 10-year experience of patients with DH diagnosed in our institution, and have reviewed the relevant literature to provide an overview of the current management of DH.

**MATERIALS AND METHODS**

During the 10 years from January 1989 to December 1999, we retrospectively analyzed data obtained from the in-patient medical records of adult patients aged >13 years diagnosed to have DH and hospitalised in Christian Medical College Hospital, Vellore, a tertiary care, teaching medical center with hospital capacity of 1750 beds. Patient demographics, socioeconomic status, domiciliary status (urban or rural), associated co-morbidities, clinical features at presentation, laboratory and imaging results, treatment and outcome of patients with DH were documented.

Inclusion criteria: Adults (age >13 years) were included as cases if: (a) histology revealed granulomas and tissue smears revealed histologically compatible, capsulated intracellular yeast like organism, and/or (b) the fungal culture revealed growth of *H. capsulatum* from tissue specimen obtained from extra-pulmonary sites (skin, mucosa, bone marrow, liver, spleen, lymph node and adrenal glands). We excluded those patients who showed granulomas on histology without identifiable organism on smear or cultures. Patients with a diagnosis of pulmonary histoplasmosis (acute and chronic) were also excluded.

Clinical course of the illness and outcome of the therapy were monitored. Patient was considered clinically cured when all clinical signs abated along with normalization of laboratory parameters and regression of initial lesions seen on imaging such as chest x-ray, CT scan and ultrasound.

**RESULTS**

Nineteen patients fulfilled the inclusion criteria. The domiciliary status of patients (statewise) was as follows: West Bengal 7, Andhra Pradesh 4, Bihar 2 and 1 each from Assam, Orissa, Uttar Pradesh, Tamil Nadu, and Kerala. One patient was from the neighboring country Bangladesh that borders West Bengal. Mean age was 42.8 years (range 13-71 years). Eighteen patients were males.

The patients were followed up from six to 37 months (mean of 19 months). The most common underlying illnesses were diabetes mellitus (5 patients) and HIV infection (4 patients). CD4 cell counts were not done for these patients. There were two renal transplant recipients and two patients were undergoing treatment for tuberculosis. Chronic obstructive airway disease and lymphoma were seen in one patient each. The remainder four patients did not have any significant co-morbid conditions.

Symptoms of significant weight loss (> 10% body weight) were seen in 89% and fever in 73%. Less commonly occurring symptoms included fatigue, diarrhoea, cough, abdominal pain, dysphagia and skin nodules. On examination, non-tender erythematous skin papules and nodules in the extremities, trunk and face were seen in two of our patients and the other signs were lymphadenopathy (31%), oropharyngeal ulcers, and hepatosplenomegaly in a third of our patients (37% and 31%) and hepatomegaly in a sixth (15%). One had isolated splenomegaly [Table 1].

Common laboratory abnormalities were anemia [Hb < 8gm%] in 8 (42%), thrombocytopenia [platelets <1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombocytopenia [platelets < 1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombocytopenia [platelets < 1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombocytopenia [platelets < 1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombocytopenia [platelets < 1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombocytopenia [platelets < 1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombocytopenia [platelets < 1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombocytopenia [platelets < 1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombocytopenia [platelets < 1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombocytopenia [platelets < 1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombocytopenia [platelets < 1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombocytopenia [platelets < 1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombocytopenia [platelets < 1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombocytopenia [platelets < 1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombocytopenia [platelets < 1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombocytopenia [platelets < 1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombocytopenia [platelets < 1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombocytopenia [platelets < 1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombocytopenia [platelets < 1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombocytopenia [platelets < 1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombocytopenia [platelets < 1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombocytopenia [platelets < 1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombocytopenia [platelets < 1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombocytopenia [platelets < 1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombocytopenia [platelets < 1,00,000/ mm³] in 7 (37 %), elevated ESR [> 50mm/hr] and hypoalbuminemia [< 8gm%] in 8 (42%), thrombo...
Clinical presentations: Our patients from 6 to 37 months) with conventional Amphotericin B and azoles (amphotericin B alone 2, azoles 6, amphotericin B followed by azoles 3). The azoles used were Itraconazole 400 mg OD for 6 months followed by 200 mg OD, Fluconazole 400 mg OD, Ketoconazole 200 mg BD till resolution of clinical and radiological abnormalities. Seven of these eleven patients had a clinical cure. In two patients, symptoms and signs improved with regression of initial lesions on imaging, and are currently being followed up. In one, relapse occurred after the patient discontinued the treatment within six months and death occurred in one, during hospital stay. Among the seven patients who did not receive treatment, six died, one patient was discharged from hospital at request and one could not be followed up.

**DISCUSSION**

This article documents the largest number of patients with DH reported from a single center in southern India. Numerous case series have reported histoplasmosis from all over India, the largest series being from Delhi, a compilation of thirty-seven patients from all over India. There are sporadic reports from Andhra Pradesh and Bihar as well. We found that 60% of our patients were from South India and 40% were from West Bengal. This seems to indicate that histoplasmosis has no particular predilection to East India as was hitherto believed.

Histoplasmosis has been reported in immunocompetent and immunocompromised individuals with the disseminated forms being more common in the latter group. The risk factors for acquiring the infection include, occupations involving disruption of soil rich in bird and bat guano like, agriculture, outdoor construction and rehabilitation of buildings inhabited by birds. In HIV infected patients, the prevalence of histoplasmosis varies from 5% to 32%, depending on the endemicity of *H. capsulatum* in these areas. Annual incidence of symptomatic histoplasmosis varies from 5% to 20%, depending on the endemicity of *H. capsulatum* in these areas. The other causes for immunosuppression in our patients included diabetes mellitus, renal transplantation and lymphoma.

The duration of symptoms prior to presentation to the hospital was 3 - 6 months. The most common symptoms seen in our series were significant weight loss, and prolonged fever as reported in other studies. The prominent symptoms of anorexia and malaise were of comparable frequency as seen with other reports. Occurrence of hepatosplenomegaly in a half, and lymphadenopathy in a third of our case series seems to be consistent with the clinical picture reported from other Indian centers.

A third of our patients had mucocutaneous lesions, which were predominantly oropharyngeal, involving...
Mycobacterium avium

<4500/cmm could help to distinguish DH from and occurs in only about 7-20%. The adrenal gland manifestation of adrenal insufficiency is uncommon, via imaging studies and autopsy findings, clinical proportion (80%) of adrenal gland affectation detected adrenomegaly in half of our patients. Despite a high and multiple intestinal hemorrhages seen in another. Another notable feature was the presence of adrenomegaly in half of our patients. Despite a high proportion (80%) of adrenal gland affectation detected via imaging studies and autopsy findings, clinical manifestation of adrenal insufficiency is uncommon, and occurs in only about 7-20%. The adrenal gland affectation may be silent or may present as unilateral or bilateral adrenal masses. This granulomatous inflammation, within the adrenals is due to a large number of macrophages amidst high concentration of steroid hormones that promotes growth of the organism. Low normal ranges of plasma cortisol were seen. The adrenal function recovers following cure with antifungal therapy unlike that seen with treatment of tuberculosis, where lifelong cortisol replacement is needed. Occasionally, with initiation of antifungal therapy acute adrenal insufficiency may be precipitated, possibly through a mechanism similar to Jarish-Herxheimer reaction. Symmers et al in 1972 described a distinct clinical syndrome “Asian Histoplasmosis” with two salient features i.e., mucosal ulceration at mucocutaneous junctions or body orifices and a propensity to acute adrenocortical insufficiency.

Hematological abnormalities such as anemia, thrombocytopenia and an elevated ESR are common and have been reported in the disseminated forms due to involvement of the bone marrow. Elevated transaminase and alkaline phosphatase levels suggest a diffuse hepatic involvement. Recent reports suggest that elevated lactate dehydrogenase levels (≥ 500 U/L), along with alkaline phosphatase ≤ 300 U/L and WBC <4500/ccm could help to distinguish DH from Mycobacterium avium complex infections in febrile patients with AIDS.

On histopathology, granulomas may be caseating or non-caseating in the self-limited forms of histoplasmosis. However, in the progressive forms of histoplasmosis, a massive influx of macrophages with scattering of lymphocytes and ill-formed granulomas may be seen. Mycelial forms are absent in tissues and this differentiates it from other moulds causing granulomatous inflammation. Granulomas commonly occur due to other chronic mycobacterial and fungal infections and hence it becomes imperative to use appropriate staining and culture techniques to identify this organism especially in the immunocompromised patients. In our study, organism was grown from 15% (bone marrow, palatal mucosa and lymph in node one each). Mycobacterium tuberculosis coexisted with histoplasmosis in two patients and was excluded by negative cultures for mycobacteria in others.

Antifungal agents reduce mortality to < 25% in those patients with disseminated histoplasmosis. Mortality without treatment can be as high as 80-100%. Treatment is indicated for all patients with progressive disseminated histoplasmosis. In our series, treatment could be initiated only in 11 of the 19 patients. Fever abatement and weight gain occurred within 4 weeks. Cure was obtained in seven, clinical improvement in two and death occurred in one. Relapse was seen in one, in whom the therapy was discontinued after 6 months. Among the eight patients in whom treatment could not be initiated, six died.

Liposomal Amphotericin B is more effective and less toxic in the treatment of DH as compared to conventional Amphotericin B and produces more rapid clearance of fungemia (though clinical response rates are similar) when compared to Itraconazole in patients with AIDS. In studies that mostly included immunocompetent hosts and specifically excluded those with AIDS, clinical response rates are 68-92% with conventional Amphotericin B, 85-100% with Itraconazole, 74-86% with oral Fluconazole and 56-70% with Ketoconazole. Even though the response rates are impressive with Fluconazole and Ketoconazole the relapse rate is as high as 30%. In AIDS the relapse rate is 80%; hence lifelong maintenance therapy Itraconazole 200 mg daily is recommended to prevent relapses. In our series also, only six patients opted for Amphotericin B and the rest were given azoles. Among the seven cured, six had received Amphotericin B.

Our study has limitations. The data we have chronicled may not represent true national prevalence or endemicity, as our center draws patients from southern and eastern regions. Being a tertiary care referral center, it may not be truly representative of the entire nation but highlights the high mortality owing to delayed diagnosis particularly in endemic areas. Practicing physicians and the patient population in endemic areas need to be informed regarding the risks of acquiring infection.

In conclusion, DH has been reported sporadically from all regions of the nation. A high index of suspicion is needed to make diagnosis sooner especially in immunocompetent hosts who are resident in endemic areas. Clinical features and laboratory features are identical to the commonly seen granulomatous infections such as disseminated tuberculosis. Oropharyngeal ulcers and adrenal gland enlargement with prolonged fever provide specific clues suggesting DH and diagnosis needs to be established via smears and/or cultures of tissues obtained from these affected tissues as early diagnosis and antifungal treatment results in remission or cure, usually with no sequelae. In those severely immunocompromised especially those
with HIV/AIDS in view of the high mortality and frequent relapse, lifelong maintenance treatment is recommended.

REFERENCES


Announcement


Highlights

- Demonstration of Surgical procedures
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Venue: Hotel Taj Connemara, Chennai.

Registration: Before 15th March: Rs. 1500/-

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Contact: Dr. V Viswanathan, Joint Director, #4, Main Raod, Royapuram, Chennai 600 013.

E-mail: drvijay@vsnl.com; Fax: 91-44-25954919