Case Report

Chronic Disseminated Histoplasmosis in a Young Immunocompetant Patient of Hypobetalipoproteinemia: A Rare Presentation

Rakesh Kumar Gupta[1], Vineeta Vijay Batra*[1], Puja Sakhuja[1], Amol Dahale[2], Amarender Singh Puri[2]

[1]Departments of Pathology, G. B. Pant Institute of Post Graduate Medical Education and Research, New Delhi, India.
[2]Department of Gastroenterology, G. B. Pant Institute of Post Graduate Medical Education and Research, New Delhi, India.

Keywords: *Histoplasmosis, Immunocompetent, Hypobetalipoproteinemia*

ABSTRACT

Disseminated histoplasmosis is commonly found in immunocompromised patients in association with acquired immunodeficiency syndrome in endemic regions but is rare in other parts of the world. We herein describe a case of sub acute disseminated histoplasmosis in a young 20-year-old lady presenting with the chief complaints of pyrexia of unknown origin, loose stools and generalized body swelling with a previous diagnosis of hypobetalipoproteinemia. Supraclavicular lymph node, bone marrow aspiration and colonic biopsy revealed numerous yeast forms of fungus histoplasma. This case illustrates that DH should be ruled out in immunocompetent non-endemic patients presenting with chronic fever even in the absence of respiratory symptoms.

***Corresponding author:**
Dr. Vineeta V Batra, Professor, Dept of Pathology, Academic Block, G. B. Pant Institute of Post Graduate Medical Education and Research, Jawaharlal Nehru Marg, New Delhi -110002
Phone: +91- 9718599075
E-mail: vvbatra9@gmail.com

Introduction

Disseminated histoplasmosis (DH) is not an uncommon disease in immunocompetent patients in India. Although three large studies and many case reports have been published from the Indian subcontinent, exact incidence is yet unknown.[1-3] It is caused by inhalation of aerosols containing hyphae of the fungus Histoplasma capsulatum. The disease usually starts with respiratory symptoms and follows a sub-acute or chronic course which commonly recovers after antifungal treatment. A high index of suspicion and timely management are of utmost importance to prevent fatal outcomes. In India where tuberculosis is the most prevalent granulomatous infectious disease, DH should be kept as a differential and fungal stains must be applied to exclude the condition, before starting empirical anti-tubercular therapy (ATT) regimen. We are presenting a case of DH in a young immunocompetent lady, previously diagnosed to have hypobetalipoproteinemia. Although hypobetalipoproteinemia is described as a risk factor for Plasmodium infection[4], till date this is the first case report of DH in association with hypobetalipoproteinemia to the best of our knowledge.

Case report

This 20-year-old female was brought to the Department of Gastroenterology with chief complaints of fever since 4 months, and loose stools, generalized body swelling and facial puffiness since 1 month. The patient had a past history of diarrhea 2 years back and was diagnosed as a case of hypobetalipoproteinemia for which she was kept on medium chain triglyceride based diet.

The fever was of intermittent onset associated with chills up to a maximum temperature of 103^0F; however symptoms of urinary tract infection, headache and cough were not present. She had a frequency of 12-15 stools/day, which were of small volume, semisolid to watery, admixed with blood and mucus in association with episodic lower abdominal pain lasting for approximately 30 minutes. History of episodes of vomiting was present. Loss of appetite and decreased body weight were also noted. There was no history of jaundice, melena, hematemesis or decreased urine output.

Routine urine examination and microscopy did not reveal any significant derangement in parameters. On examinationa left supraclavicular firm, mobile and non-tender lymph node, measuring 2x2 cm was found. Both liver and spleen were palpable. Shifting dullness was also noted. All the vitals were within normal range.

A battery of investigations were conducted which revealed the following results (Table 1).Blood lipid profile showed severe derangement of total cholesterol, low density lipoprotein, triglyceride and high density lipoprotein. All primary causes of hypobetalipoproteinemia were excluded by the normal thyroid profile, negative viral serology (especially HCV), negative family history and non-alcoholic status. A final diagnosis of secondary hypobetalipoproteinemia (based on lipid profile values less than 5th centile for the normal same age/sex person) was considered; most probably malabsorption.

Colonoscopy showed multiple whitish plaques up to terminal ileum (Fig 1A) which on biopsy revealed sheets of yeast forms of H. capsulatum (Fig 2). The patient was put on liposomal amphotericin-B (150 mg OD) and showed a slight improvement; however her dyspnea worsened after a week. A repeat chest X-ray revealed bilateral hilar infiltrates (Fig 1B) which was suspected to be co-infection by Pneumocystitis carinii and cotrimoxazole was started simultaneously. The patient did not respond to these antibiotics and cotrimoxazole was replaced by meropenam. Despite all measures, dyspnea worsened and patient developed hypotension which was managed by intravenous inotropes, hydrocortisone and ventilator support. She underwent a cardiac arrest on day 17 and succumbed to her illness.

Discussion

DH is a well-known entity in immunocompromised patients especially in AIDS; however many cases have been also reported in immunocompetent individuals mainly from endemic regions of the world. [5,6] In India, the first case of DH was described by Panja and Sen in 1954. [6,7] Several risk factors have been illustrated including malignancies, organ transplant, drugs like anti TNF-α and steroids, diabetes mellitus, chronic lung diseases and extremes of age. Gopalakrishnan and Subramanian in their studies described diabetes and AIDS as common co-morbid conditions. [2, 3]

Hypobetalipoproteinemia is identified as a risk factor for malarial parasite infection. However it has not been described as a risk factor for DH till date. [4] Hypocholesterolemia accompanying infections has been suggested as a poor prognostic marker in hospitalized patients and may be associated with low serum antioxidant reserve, possibly increasing susceptibility to oxidative stress.[8]

DH is caused by thermally dimorphic fungus H. capsulatum which is found in soil particularly rich in bird droppings. Persons engaged in activities involving handling of soil/ materials rich in bird and bat droppings such as agriculture, construction and rehabilitation of old buildings are particularly at risk of acquiring infection.

Table 1: Clinical Investigational Profile of the Patient

Haemogram	Hb-7.3 gm/dl TLC-1465/µl DLC-P_{67} L_{25} M_6 E_2 Platelets-49000/µl
Peripheral smear	RBCs-normocytic, normochromic, occasional macrocytes
Liver function test	Bilirubin (total)-0.9 mg/dl AST/ALT-30/20 IU/l TP/Albumin-3.2/2.2 g/dl INR-2.2
Serum lipid profile	TC-27 (N:100-190) mg/dl, TG-34 (N: <150) mg/dl, HDL-6.9 (N: >40) mg/dl, LDL-13.5 (N:100-120) mg/dl
Thyroid function test	TSH-1.74 (N: 0.5-5.5) mIU/l
Viral serology (Hepatitis B, Hepatitis C, HIV)	Non-reactive
Immunoglobulin profile	WNL; IgG-700 (N: 700-1600) mg/dl, IgM-49 (N: 40-230) mg/dl, IgA-105 (N: 70-400) mg/dl
Stool (Routine & Microscopy)	Few RBCs, no ova/cyst
Urine routine & microscopy	Protein- nil, Epithelial cells-0-1, RBCs – nil, casts- nil
Urine culture	Sterile
Blood culture	Sterile
Ascitic fluid	40 cells (lymphocytes), protein-0.5, SAAG-1.8
Chest X-ray (initial work-up)	NAD
Chest X-ray (a day before death)	Bilateral hilar infiltrates
ECG	NAD
USG abdomen	Liver 16.4 cm with coarsened echo texture Spleen 14.7 cm, PV- 10.4 mm Moderate ascites
Upper gastro-intestinal tract endoscopy	Normal
Colonoscopy	Multiple whitish plaque till terminal ilium
Doppler/USG lower limbs	No evidence of DVT
FNAC supraclavicular lymph node	Yeast form of Histoplasma
Rectal biopsy	Yeast form of Histoplasma
BMA cytology	Yeast form of Histoplasma
Post-mortem liver biopsy	Yeast form of Histoplasma
TLC- total leucocyte count; DLC- differential leucocyte count; NAD-No abnormality detected; WNL- within normal limit; DVT-deep vein thrombosis; FNAC-fine needle aspiration cytology; BMA-bone marrow aspiration	

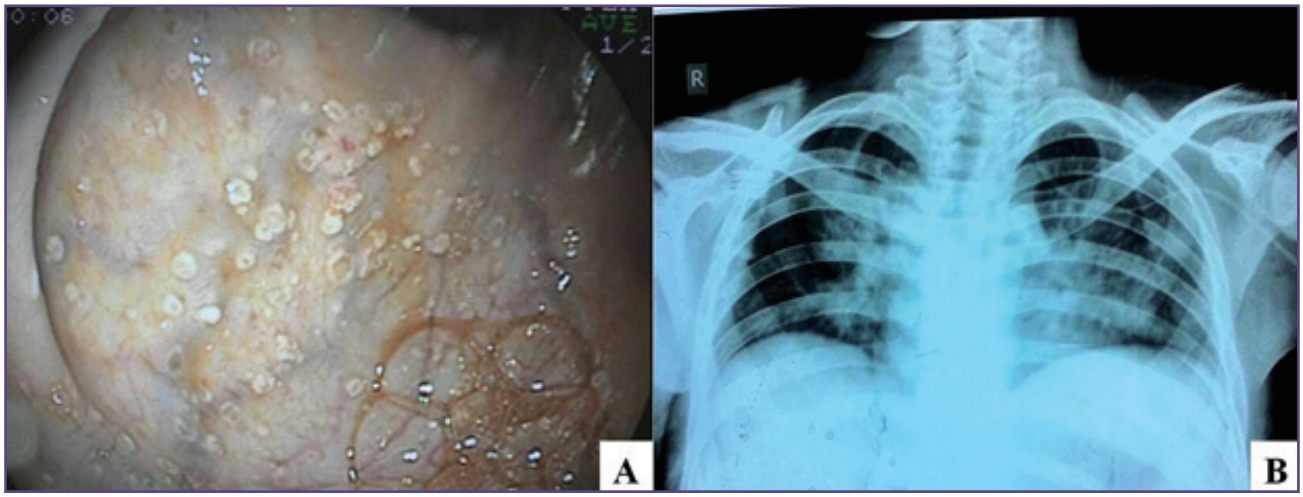

Fig.1 A: Colonoscopy showing multiple whitish plaques in the colonic mucosa.
Fig.1 B: X-ray chest PA view showing bilateral hilar infiltrates in the lungs a day before patient succumbed.

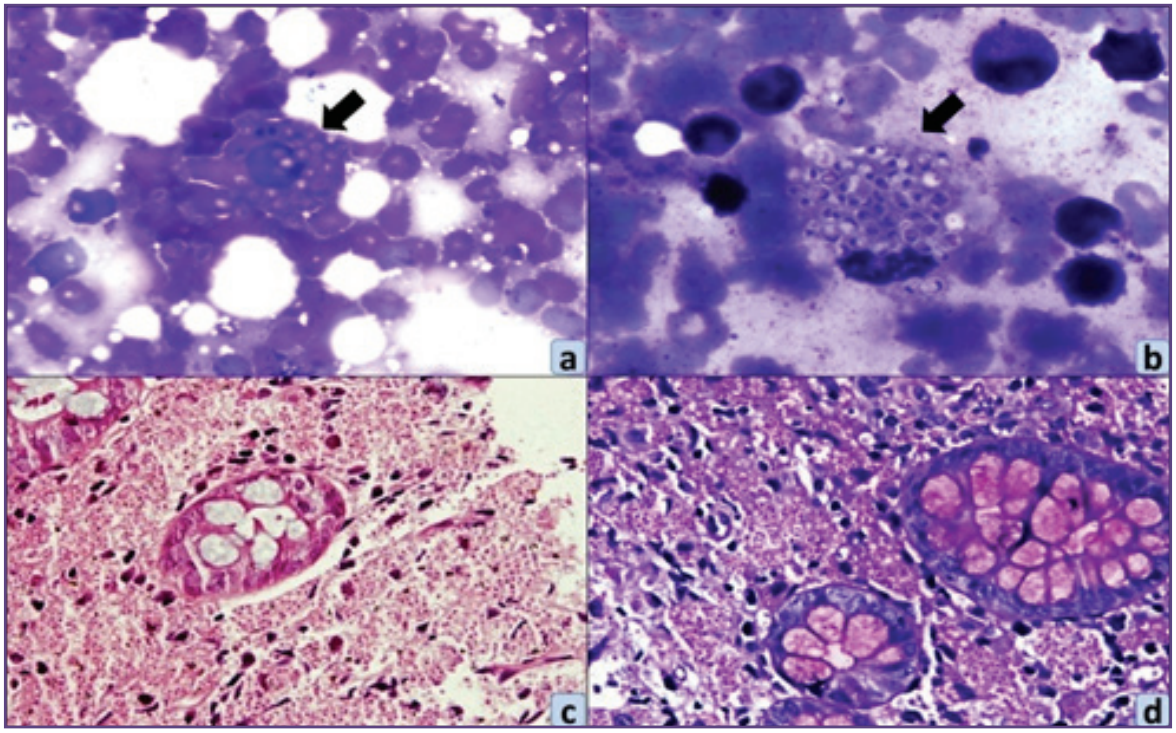

Fig. 2: Photomicrographs showing both intracellular and extracellular yeast form of H. capsulatum (black arrow): supraclavicular lymph node (a: Giemsa x600), bone marrow aspiration (b: Giemsa x1000 oil immersion), colonic biopsy (c: HE x400), (d: PAS x400).

Histoplasmosis can clinically present as acute pulmonary histoplasmosis, chronic pulmonary histoplasmosis or progressive disseminated histoplasmosis. [7] The usual manifestations include fever, malaise, headache, skin lesions, cough, dyspnea, oropharyngeal ulcers, lymphadenopathy, hepatosplenomegaly and Pancytopenia. [9] The respiratory system being the most common portal of entry is involved early in the course of the disease followed by other organ systems. However the present case manifested with gastro-intestinal symptoms. Colonoscopy revealed multiple white plaques involving rectum, colon and part of terminal ileum similar to a case report by Colaiacovo et al.[10]Although adrenal enlargement is frequently noted in DH, signs of adrenal involvement were absent on imaging in the present case.

Histoplasmosis can be diagnosed by culture, antibody titers and tissue biopsy. A delay in the diagnosis of DH may result in the exacerbations of symptoms and flaring-up of the infestation. In the three large studies from India, most patients recovered after adequate treatment with only one death being reported.[2] In present study, the patient succumbed within 17 days after admission.

Conclusion

DH should always be ruled out in immunocompetent non-endemic patients presenting with chronic PUO, weight loss and diarrhea, even in the absence of respiratory symptoms. DH can result in fatal outcome unless managed timely with appropriate therapy. Hypobetalipoproteinemia may be a possible risk factor for DH, similar to malarial parasite, however a large cohort study is essential for confirmation of this finding.

Acknowledgment

We would like to acknowledge Dr Kaushik Majumdar for his help and support in compilation of figures.

Conflict of interest and Source of funding

None

References

1. Randhawa HS, Khan ZU. Histoplasmosis in India: Current Status. Indian J Chest Dis Allied Sci1994; 36:193-213.
2. Subramanian S, Abraham OC, Rupali P, Zachariah A, Mathews MS, Mathai D. Disseminated Histoplasmosis. J Assoc Physicians India 2005; 53:185-9.
3. Gopalakrishnan R, Nambi PS, Ramasubramanian V, Abdul Ghafur K, Parameswaran A. Histoplasmosis in India: truly uncommon or uncommonly recognised? J Assoc Physicians India 2012; 60:25-8.

4. Badiaga S, Barrau K, Parola P, Brouqui P, Delmont J. Contribution of nonspecific laboratory test to the diagnosis of malaria in febrile travelers returning from endemic areas: value of hypocholesterolemia. J Travel Med. 2002; 9:117-21.
5. Wheat LJ, Kaufman CA. Histoplasmosis. Infect Dis Clin North Am. 2003; 17: 1–19.
6. Panja G, Sen S. A unique case of histoplasmosis. J Ind Med Assoc.1954; 23:257.
7. Sane SY, Patel MG, Patel BM, Kokal KK. Disseminated histoplasmosis (a case report). J Postgrad Med.1983; 29:270–273.
8. Muldoon MF, Marsland A, Flory JD, Rabin BS, Whiteside TL, Manuck SB. Immune system differences in men with hypo- or hypercholesterolemia. Clin Immunol Immunopathol. 1997; 84:145-9.
9. Kauffman CA. Histoplasmosis. In: DismukesWE, Pappas PG, Sobel JD. Clinical mycology. New York: Oxford University Press; 2003: 291.
10. Colaiacovo R, de Castro AC, Shiang C, Ganc RL, Ferrari AP Jr. Disseminated histoplasmosis: a rare cause of multiple ulcers in the gastrointestinal tract. Endoscopy 2011; 43:E216.