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RARE PRESENTATION OF DISSEMINATED HISTOPLASMOSIS IN IMMUNOCOMPETENT INDIVIDUAL

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ABSTRACT Histoplasmosis is fungal disease caused by Histoplasma capsulatum in endemic area. In India, the most cases reported from eastern India considered to be endemic for the disease. The causative fungus persists in soil, infects through inhalation and manifests in three main types-acute primary, chronic cavitary and progressive disseminated histoplasmosis. Disseminated Histoplasmosis (DH) is defined as a clinical condition where the fungus is present in more than one location. Among the forms of histoplasmosis, DH is the rare and mostly found in an immuno-compromised individual. In this paper we report three cases of disseminated histoplasmosis in immuno-competent patients from Rajasthan.

KEYWORDS : Disseminated Histoplasmosis (DH), Histoplasma capsulatum, Autoimmune Hemolytic Anemia (AIHA), Myelofibrosis.

INTRODUCTION

Histoplasma capsulatum, a thermal dimorphic fungus. Soil enriched with bird or bat droppings promotes the growth and sporulation of Histoplasma. Contaminated soil can be potentially infective for years. Human infection is acquired by inhalation of mycelia form. Clinically it manifest as three main types-acute pulmonary,chronic pulmonary and progressive disseminated histoplasmosis [1]. DH is the rare form and usually found in immuno-compromised individuals. The disease is endemic in certain regions of Latin America and North America. In India, Histoplasmosis is endemic in eastern region (West Bengal and Assam), particularly in the Gangetic delta.[2] The first case of DH was reported by panja and sen from Calcutta in 1954.[3] Later on many sporadic cases have been found both from North India as well as South India. This pattern of distribution may be related to climate, humidity level, and soil characteristics. Here we are presenting our experiences of the series of cases of DH in immuno-competent individuals.

CASE 1

A 30-year-old male patient was admitted in SMS hospital, Jaipur with complaints of high-grade fever, chills, rigors and sweats of 1½ month duration. There was also h/o dry cough for past 20 days. On general examination, the positive findings were fever, pallor and icterus. A systemic examination revealed a soft abdomen with non tender palpable liver(4cm) and a tender palpable spleen(4cm). Rest of systemic examinations were normal.

Laboratory investigations revealed pancytopenia. PBF and reticulocyte count was normal without any atypical cells. Malarial by antigen and peripheral smears (thick and thin) was negative. Widal and dengue IgM & IgG were negative. HIV 1 and 2 ,HBsAG ,AntiHCV were negative. Urine examination was normal. LFT showed mildly elevated liver enzyme levels—SGOT (AST)—87 U/l, SGPT (ALT)—72 U/l, ALP—235 U/l and LDH—4650 U/l. Serum electrolytes and RFT was normal. Chest x-ray appeared to be normal, but CECT thorax showed multiple ill defined confluent patches of ground glass haziness in b/l lung fields ?interstitial pneumonitis, also multiple enlarged lymphnodes were noted in b/l axilla, prevascular, preand paratracheal region. UGS and CECT abdomen revealed hepatosplenomegaly.

Sputum for AFB, gram stain and KOH mount was negative. Blood and urine culture yielded no growth. Next a autoimmune workup showed positive CRP, negative ANA and positive direct coombs suggesting autoimmune hemolytic anemia (AIHA). Next to rule out cause of fever and pancytopenia a bone morrow biopsy was done. BM examination showed dimorphic erythroid hyperplasia with hypercellular bone marrow with intracellular and etracellular capsulated yeast which was PAS and MSN positive suggestive of H.capsulatum . Later Liver biopsy was done which showed mild increase in lymphocytes with kupffer and stellate cells packed with histoplasma organism which was PAS and MSN stain positive. So a final diagnosis of disseminated histoplasmosis with autoimmune hemolytic anemia (AIHA) was done.

CASE 2

A 60-year-old male patient was admitted with history of fever, dry cough, pallor and fatigue for 2 months. He also had history of skin lesions over abdomen and back for past 1½ months with significant past history of pulmonary tuberculosis 10 years back. There was no history of any other comorbid illness. On general examination, patient was febrile and pale. Papulonodular skin lesions with superficial ulceration were seen over abdomen and back. A systemic examination revealed a soft abdomen with non tender palpable liver and spleen.

Lab investigations showed pancytopenia, normal PBF and a low reticulocyte index. LFT was deranged, Malarial by antigen and peripheral smears (thick and thin) was negative. Widal test and dengue IgM & IgG were negative. HIV, HbsAg and anti HCV were negative. CECT thorax revealed cavitatory lesion with fibronodular consolidation in right upper lobe- likely infective etiology? koch's. USG and CECT abdomen showed hepatosplenomegaly with splenic infarct. Sputum for AFB, gram stain and KOH mount was negative. Blood and urine culture yielded no growth. Autoimmune workup was negative (CRP ,RF, ANA).Even after these above investigations no cause was found and a provisional diagnosis of pyrexia of unknown origin was made and was further investigated. Next, bone marrow aspiration was done, which was normocellular but biopsy revealed fibro fatty tissue and fibrosis, few focal areas of normal hematopoiesis and reticulin were also seen, suggestive of myelofibrosis. Meanwhile a punch biopsy of skin showed tissue reaction in the form of necrosis and granulomatous changes suggestive of tuberculosis or deep fungal infection.Later Liver biopsy was done which showed histiocytes filled with PAS and MSN stain positive Histoplasma organisms. So, a final diagnosis of disseminated histoplasmosis with secondary myelofibrosis was made.

CASE 3

A 55-year-old male patient was admitted with complaints of moderate to high-grade fever, not associated with chills and rigor, of 3 month duration with multiple oral ulcers for 2 months. On general examination, patient had fever, multiple superficial ulcers over tongue and buccal mucosa. One more ulcer with superficial scar seen over left leg. A systemic examination revealed a soft abdomen with non tender palpable liver (4cm) and a non tender palpable spleen(3cm). Rest of systemic examinations were normal.

Laboratory investigations showed normal complete blood counts. PBF was normal without any atypical cells. Malarial by antigen and peripheral smears (thick and thin) was negative. Widal and dengue IgM & IgG were negative. Antibodies for HIV 1 and 2 were not detected.

Urine examination, LFT, RFT and Serum electrolytes were normal. Chest x-ray appeared to be normal, but CECT thorax showed partially calcified mediastinal and bilateral hilar lymphadenopathy. UGS and CECT abdomen revealed hepato-splenomegaly.Sputum for AFB, gram stain and KOH mount was negative. Blood and urine culture yielded no growth. Next a autoimmune workup showed positive CRP, negative ANA.

Next to rule out cause of fever a bone morrow biopsy was done. BM examination showed hypoplastic marrow without any evidence of hemoparasite or granuloma. Liver biosy done later showed portal tracts filled with lymphoplasmacytic cells and histiocytes, having intracytoplasmic round bodies positive for MSN staining suggestive histoplasmosis.

So a final diagnosis of disseminated histoplasmosis was done.

Liver Biopsy

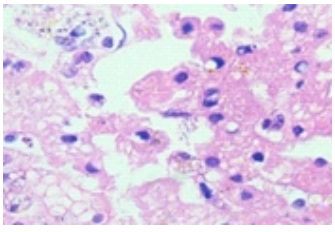


Figure 1: H&E Stain

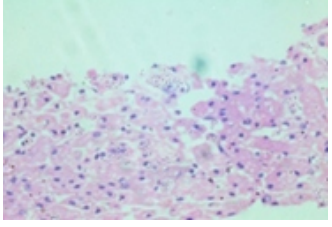
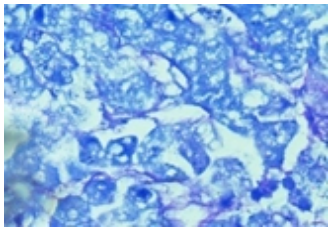


Figure 2: PAS



Bone Marrow Biopsy

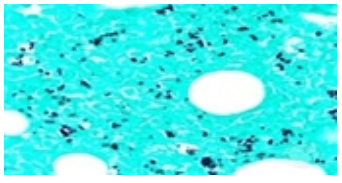


Figure 4: MSN Stain

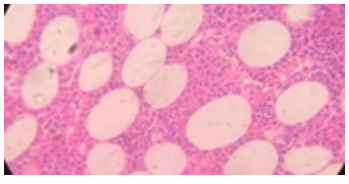


Figure 5: H&E Stain

DISCUSSION

	CASE 1	CASE 2	CASE 3
AGE/SEX	30/M	60/M	55/M
CLINICAL PARAMETERS			
FEVER	11/2 month	2month	3month
RESPIRATORY SYSTEM	Dry cough	Dry cough	Absent
SKIN INVOLVEMENT	Absent	Papulonodular skin lesion	Multiple oral ulcers
HEPATOSPLENOMEGALY	Present	Present	Present
LYMPHADENOPATHY	Absent	Absent	Absent
PALLOR	Present	Present	Absent
LABORATORY INVESTIGATION			
Hb(gm/dl)	4.5	6.5	13.6
TLC	1600(N-60%,L-37%)	3000(N-58%,L-39%)	8500(N-67%,L-28%)
PLATELET	56000	45000	3.2LAC
LFT(OT/PT/LDH)	87/72/4650 U/L	159/111/565 U/L	42/34/234 U/L
AUTO IMMUNE TEST	ANA –VE/ +VE COOMB'S AND CRP	CRP , ANA –VE	CRP ,ANA –VE
BONE MARROW EXAMINATION	Hypercellular with histoplasmosis	Myelofibrosis	Hypoplastic
LIVER BIOPSY	Histoplasmosis	Histoplasmosis	Histoplasmosis

Table 1: Details of clinical and laboratory parameters of patientsHistoplasmosis is not rare disease in India, but diagnosed less commonly. Three large studies, from Delhi and South India, reported an occurrence of 37, 24 and 19 DH respectively, in 10 year follow up period.[4,5,6] The majority of patients were from Gangetic Delta, where it is endemic. The present study is from a tertiary care centre from eastern Rajasthan, which is not an endemic area for histoplasmosis. DH usually occurs in immuno-compromised individual.Although, study from CMC Vellore has shown a high prevalence of DH in immuno-competent hosts.[5] Sometime histoplasmosis may cause PUO which remain undiagnosed. This case series also shows the incidence of DH as a cause of PUO in immuno-competent individual.

Histoplasmosis manifest as three main types:

1. Acute pulmonary histoplasmosis

It is usually a self-limited illness. Symptoms include fever, headache, malaise, weakness; substernal chest discomfort and dry cough. [7] Chest X-ray may show a patchy pneumonia with enlarged hilar and mediastinal lymph nodes . Improvement is usually rapid .[8,9]

2. Chronic pulmonary histoplasmosis

This type occurs mostly in elderly patients with underlying lung disease accompanied with fever, cough, malaise and weight loss for more than 3 months'. [1]It usually involves the apical segments near emphysematous bullae. Pleural thickening is frequently seen. [10] Progressive dyspnea, sputum production, and hemoptysis, are common symptoms if cavitatory lesion are present.

3. Progressive disseminated histoplasmosis

It is a condition where the fungus is present in more than one location. DH usually occurs in immuno-compromised hosts (infant, AIDS with CD4 count < 150 cells/µL, hematologic malignancy ,solid organ transplantation, use of corticosteroids and tumor necrosis factor antagonists). H.capsulatum may remain dormant and reactivation may occur years after initial exposure.[11]

The most common signs and symptoms are fever, shivering, indisposition, weight loss, hepatomegaly, splenomegaly, peripheral lymphadenopathy; ulceration of oropharyngeal mucosa (in 25–75% of cases); bone marrow alterations (anemia, leukopenia, thrombocytopenia) [12].In our case series bone marrow alteration present in two cases with secondary myelofibrosis in 2nd case which is very rare. Liver involvement present in all 3 csaes. Liposomal Amphotericin B is more effective and less toxic in the treatment of DH as compared to conventional Amphotericin B [1] . In our study, both liposomal Amphotericin-B was given for 14 days and then Itraconazole 200 mg twice daily for 12 month.symtomatic improvement occurs after 10 days with normal hematological parameter with negative coomb's test after 1 month.In second case hematological parameter improved after after 6 month . Repeat bone marrow show significant improvement

CONCLUSION:

In countries like India, where the prevalence of TB is high, clinical diagnosis of DH is often not suspected. Though majority of patients of DH are immunocompromised, the diagnosis should also be suspected in an immunocompetent host with PUO, as highlighted in our cases.

DH may cause secondary myelofibrosis and auto immune hemolytic anemia which is very rare

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