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KEYWORDS:
Histoplasmosis, Brain Radioogy, pancytopenia, bone marrow, Special stains, immunocompetent.

INCIDENTALLY DIAGNOSED DISSEMINATED HISTOPLASMOSIS AMONG NON HIV PATIENTS OF SOUTH ASIAN REGION.

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ABSTRACT

Background –
Histoplasmosis is a soil based rare air borne fungal infection and mostly documented in HIV positive patients. They are common in people living near valley region.

Materials and methods–
This is a multiinstitutional study. We report 3 cases of asian women from different regions of Southern Rajasthan who died due to delayed diagnosis of Histoplasmosiswithin few days of admission. They all had complaints of fatigue and fever since 1 month. One presented with decreased urine output and pancytopenia. Others had complaints of prolonged fever with pancytopenia and fatigue. All were diagnosed on Bone marrow examination for presence of Histoplasma Capsulatum, diagnosis was supported by special stains used for reporting. Treatment was started but patients deteriorated and died within 10 days of admission.

Conclusion-
Delay in diagnosis of Histoplasmosis leads to death of patients. So, Histoplasmosis is considered as a differential diagnosis of prolonged fever with pancytopenia and chronic infections.

INTRODUCTION:

Histoplasmosis is caused by a dimorphic fungus Histoplasma Capsulatum. It is of 2 types – Histoplasma capsulatum var. capsulatum and histoplasma capsulatum var. Duboisii causing disease in humans (1). Histoplasmosis is defined according to the European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) in 2008. It is a disease in which *Histoplasma spcs.* Is found positive in any culture or is confirmed by histopathology of blood, bone marrow or any other infected sites. If a patient demonstrates involvement at a single site and lacks symptoms or signs of systemic involvement, the disease is defined as focal histoplasmosis. Disseminated histoplasmosis is diseased state, when *Histoplasma capsulatum* is present in blood and bone marrow or the fungus is confirmed from multiple normal sites in the organism. In disseminated histoplasmosis, early diagnosis is the key to save the patient.

Most of the infected individuals remain asymptomatic and does not get diagnosed for histoplasmosis and die. Chronic progressive disseminated histoplasmosis has been mostly described in older and AIDS positive patients (2, 3, 4, 5). It is common opportunistic infection in AIDS positive patients (6, 7,8,9) .The time course of the infection in these patients is of months, but if not treated can be fatal for patients. We present 3 cases of HIV negative 40-45 years old females with common complaints of fatigue and pancytopenia residing in Southern Asia regions at different centres.

Case presentations:

Case 1

A 42 year old female with old medical history of Diabetes Mellitus II and Hypertension was admitted in hospital with complaints of decrease urine output, fatigue, diminished vision and pedal swelling. Patient was on Insulin and other hypertensive drugs. She had single blood transfusion history few days back at some small centre.

On physical examination patient was pale, had bilateral pedal swelling with increased respiratory rate, blood sugar and blood pressure.

On Ocular examination diabetic retinopathy was present.

Laboratory investigations are as follows –
Complete blood hemogram report reveals pancytopenia with Hemoglobin level – 5.8 gm, platelet count – 70,000, Total leukocyte count – 2000/cumm. Urine output was less and shows proteinuria with puss cells. KFT was deranged with increased creatinine level, LFT was normal and rest other parameters were within normal limit.

Chest Xray report was normal, Usg abdomen shows contracted kidney with mild hepatosplenomegaly which further aggravates to moderate splenomegaly in repeated USG report done after 3 days.

On subsequent days patient started complaining for shortness of breath with altered sensorium. CSF analysis was done, which was normal. Peripheral smear was morphologically normal with pancytopenia. Bone marrow examination was done subsequently which reveals small budding intracellular yeast colonies showing "halo" effect around each organism and hematooxylinophilic nuclei stained with H&E stain. PAS and GMS stain were done on bone marrow biopsy slides which show positive intracellular colonies and thus confirms presence of Histoplasma capsulatum in Bone marrow.

Case 2

We report a case of a 69 year female came to medicine Opd with complaints of prolonged fever, shortness of breath and fatigue since 1 month. She was immunocompetent. There were no history of Diabetes and Hypertension. She was examined and investigated. On physical examination she was pallor and respiratory rate was raised. Her B.P and pulse was normal.On blood investigations – CBC report reveals pancytopeniawith Hemoglobin – 10mg/dl, Platelet count – 14000/cumm, TLC – 3000/cumm. Random blood sugar was 273, LDH was raised and Dengue NS1 antigen was positive. Rest all parameters were normal. Kft, LFT, procalcitonin level, urine examination were normal.Bone marrow aspiration and biopsy both were positive for intracellular fungal elements in macrophages, positive for histoplasmosis.On radiological investigations – Chest Xray depicts normal findings.

Usg Whole abdomen was also unremarkable. CT Brain showed mild periventricular hyperdensity in right parietal regions, possibly soft calcifications.

This patient was shifted to Respiratory ICU within 2 days and her condition keeps on deteriorating and finally she died within 10 days of admission. Mean while she was treated for Tuberculosis and dengue with steroids and fluid infusion.

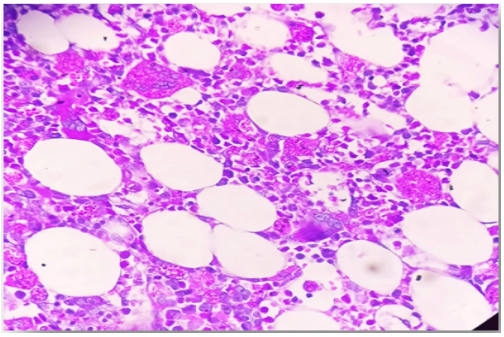

Figure (c) Pas positive histoplasma at 40x

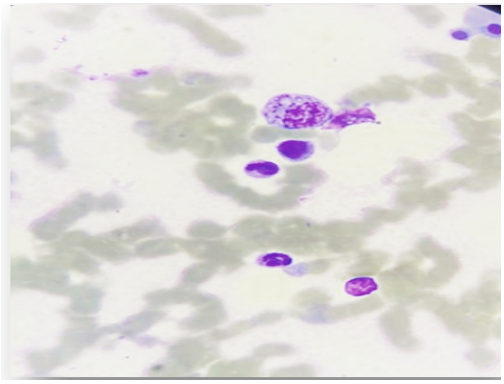

Fig. c and Fig. a

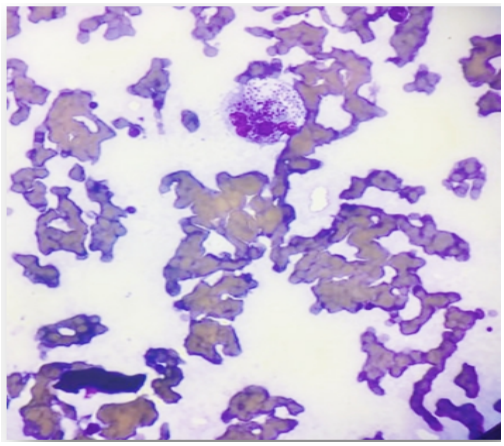

Fig. b

Figure (a) and (b) H&E stain showing intracellular bodies in macrophages at 40x and 100x.

Case 3-

Another case was reported in same duration at Jodhpur government hospital, 48 yr old female reported with breathlessness, fever and fatigue was admitted to ICU and all investigations were sent, CBC reveals Pancytopenia, along with raised LDH. Her Chest X-ray shows diffuse areas but rest all investigations were normal. She had short history of cough and breathlessness. Steroids were started, but no improvement was observed.On bone marrow examination same morphology as of Histoplasma was found. Subsequently seizures developed for which MRI brain was suggested, findings are as explained below figure d,e,f. Thus antifungals were started, her CBC improved but she died within 2 days.

Thus again delay in diagnosis and refrainment from antifungal therapy lead patients death.

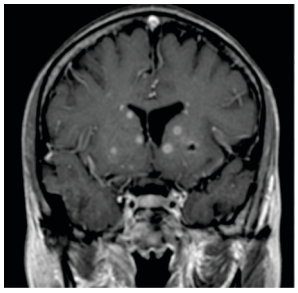

Figure d.

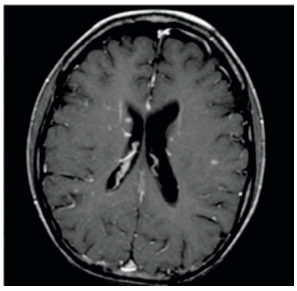

Figure e.

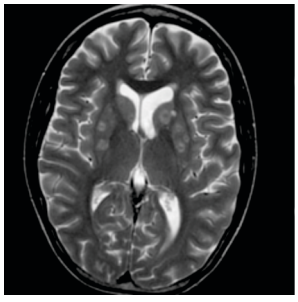

Figure f.

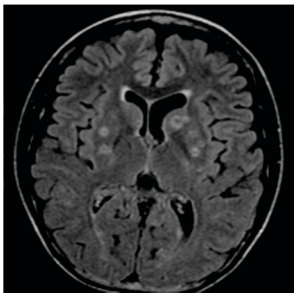

Figure g.

Thegiven MRI images shows multiple tiny 2 flair hyperintense lesion which on post contrast scans shows ring enhancement predominantly noted in the basal ganglia,grey matter,central portion of the cerebellum,few of them shows perilesional edema.

DISCUSSION:

We report cases of histoplasmosis in a 4th decade females. When these patients were admitted, we did not consider histoplasmosis as a diagnosis. Humans acquire this infection through inhalation of microconidia of yeast. Most infected persons also experience a hematogenous spread of organism to reticuloendothelial organs such as liver, spleen, bone marrow etc. (3). One review study done in South Asia by Wang et al (10).On Disseminated Histoplasmosis noticed that none of reports initially considered Histoplasmosis as early diagnosis. We also considered chronic kidney disease as cause of bone marrow suppression causing pancytopenia. Dialysis was done of first case and her renal picture improves. Her creatinine level lowers down, but in contrary her clinical condition does not improved. She develops altered sensorium, breathlessness, anorexia and her oxygen level also started drooping down. In other patients fluids and steroid therapy was given as foe dengue and breathlessness .Subsequently along with other therapies there bone marrow work up was also started. On bone marrow examination, aspiration reveals presence of intracellular yeast colonies with "halo" effect residing inside macrophages as shown in figure (a,b)at 40x and 100x known as Hemophagocytosis phenomenon (11). Bone marrow biopsy shows fungal filaments. Although Histoplasmosis can be confused with Cryptococcus and Blastomyces dermatitidis, but they can be differentiated on the basis of the feature that cryptococci are carminophilic and Blastomyces cells are multinucleated, thick walled and bud from a base. The most important differentiating feature is only Histoplasma are PAS and GMS positive shown in figure (c) at 40x while other fungi give negative response to these special stains. Two patients among them had history of previous blood transfusion and i.v. iron transfusion at some small centres. When diagnosis was made liposomal Amphotericin B was adviced to patient but unfortunately patients die. Things to ponder are that lungs of first 2 cases were absolutely normal till end, infection spread rapidly among all

tissues. Within 10 days of admission all patients die. They develop moderate hepatosplenomegaly at end. If diagnosis could make early, the patient can be saved. Therefore, Histoplasmosis should be considered as differential diagnosis among patients of chronic kidney disease along with any immunocompromised diseases (12).

CONCLUSION:

Patients with Histoplasma infection are predominantly women. There is no age and immune status criteria defined for this deadly infection. So, patients with prolonged fever and pancytopenia should be evaluated for histoplasma infection devoid of looking rareness and immunity status of affected ones. In above all cases medical fraternity failed to save the patients due to delayed diagnosis.

Disseminated histoplasmosis should be considered as differential in patients of chronic kidney disease, breathlessness, and multiple blood transfusion history along with pancytopenia and should be treated early. So that they can be saved. As this deadly disease does not cares about age and time of patient, disseminates rapidly. So. as per epidemiological records of histoplasmosis near valley regions can be challenged as these case were reported in dry areas and in same time duration of November to January months.

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Conflicts of interest - There are no conflicts of interest.

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