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Laboratory Medicine

DISSEMINATED HISTOPLASMOSIS MIMICKING MILIARY TUBERCULOSIS DIAGNOSED ON BONE MARROW ASPIRATION STUDY: A CASE REPORT AND REVIEW

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ABSTRACT We report a case of a patient who presented with low grade fever, weight loss, cough, decreased appetite, loose stool and worsening of breathlessness for 1 year. He was on antitubercular treatment 6 months before (for radiologically diagnosed miliary TB) and he discontinued the medication thereafter. On investigation patient was found to have pancytopenia, bone marrow aspiration was done which revealed intracellular yest in macrophages. Patient was found to be HIV positive on serology. Given the clinical presentation, bone marrow findings and immunosuppression patient was diagnosed with disseminated histoplasmosis and started on anti retroviral and antifungal drug.

KEYWORDS : Histoplasmosis, disseminated histoplasmosis, Miliary tuberculosis

CASE REPORT

A 47-year-old male presented in the Medicine OPD of FAAMCH with low grade fever, weight loss, cough, decreased appetite, loose stool and worsening of breathlessness for 1 year. He was on antitubercular treatment 6 months before (for radiologically diagnosed miliary TB) and he discontinued the medication thereafter. On clinical examination, he was hypotensive (90/60mm Hg), with a respiratory rate of 23/min, had pallor and was malnourished with wasting. On CBC and PBS examination, pancytopenia was noted, for which bone marrow aspiration cytology was done. Bone marrow examination revealed intracellular yeast cells of Histoplasma capsulatum. On subsequent evaluation, he was found to be serology positive for Human immunodeficiency virus.

LABORATORY TEST RESULTS PRIOR TO HOSPITAL ADMISSION: Radiological examination: HRCT thorax (Figure 1) revealed multiple tiny opacities distributed over bilateral lung

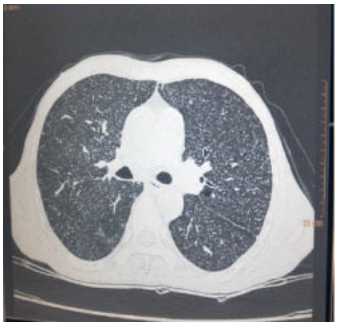

Fig:1: CT image of lung showing miliary mottling.

fields features suggestive of miliary tuberculosis. Sputum: Sputum AFB and Gene Xpert were negative.

LABORATORY TEST RESULTS POST HOSPITAL ADMISSION: Blood biochemistry: Liver function test (Total bilirubin 6 mg/dl, Unconjugated bilirubin 4.3 mg/dl, AST-98 IU/L, ALT – 28 IU/L, AlkP – 217 IU/L, S. Albumin – 1.5 g/dl, Globulin – 3.2 g/dl).

COMPLETE BLOOD COUNT:

WBC 2070/µl, RBC 2.47×106 /µl, HBG 4.7g/dl, HCT 13.9%, MCV 56.3fL, MCH 19 pg, MCHC 33.8g/dl, PLT 40×103 /µl, RDW-CV 21.5%. Differential count: Neutrophils 55% Lymphocytes 43% Monocytes 1% Eosinophils 0.5 %, Basophils 0.5% ESR: 33mm at the end of 1st hour, Reticulocyte count 3.5%

PERIPHERAL BLOOD SMEAR

RBC series shows predominantly microcytic hypochromic RBCs. Marked anisocytosis is noted with presence of occasional polychromatic RBCs. Occasional NRBCs seen. No hemiparasites seen.

WBC series shows moderate leukopenia, No immature cells seen. Platelets are reduced in number and normal in morphology

BONE MARROW ASPIRATION

Bone marrow aspiration smear showed marked erythroid hyperplasia with presence of intracellular inclusions in the macrophages.

At this stage histoplasma, leishmaniasis, and other yest infections were considered in differential diagnosis.

Morphologically leishmaniasis and other yeast infections were ruled out. Marrow material was sent for culture.

Given the clinical presentation, bone marrow findings and immunosuppression patient was diagnosed with disseminated histoplasmosis and started on anti retroviral and antifungal drug.

Despite optimal treatment the patient died 3 days after admission to hospital.

The diagnosis of histoplasma capsulatum was subsequently confirmed by culture.

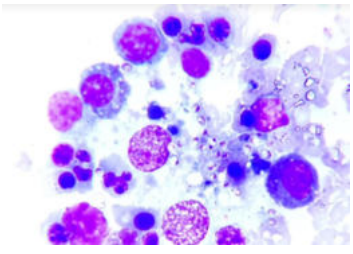

Fig:2: MGG stained smear showing Intracellular yest form

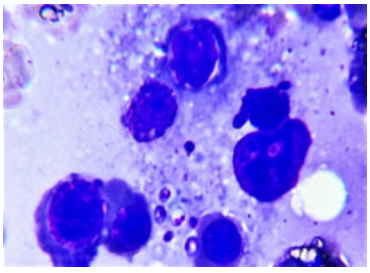

Fig:3: MGG stained smear show intracellular yest form.

REVIEW OF LITARATURE

INTRODUCTION

Histoplasmosis is a rare fungal disease caused by dimorphic fungi Histoplasma capsulatum. There are two different varieties, var. duboisii and var. capsulatum. [1]

Like most fungal infections, histoplasmosis is common in immunocompromised patients. In immunocompetent patients, infection is generally asymptomatic and rarely turns into a disseminated form.[2]

Diagnosis is usually made on suspicion from tissue specimen or aspirate cytology from the lymph node, bone marrow, or organ involved showing an intracellular yeast form especially in sections stained with giemsa stain or PAS (Periodic acid Schiff) or Gomori methenamine silver stain. Culture in Sabouraud's dextrose agar is confirmatory.[3]

EPIDEMIOLOGY

In India, Histoplasmosis is endemic in Assam, West Bengal and particularly in the Gangetic delta. Many sporadic cases have been found both from North India as well as South India.[1]In India the majority of histoplasmosis cases were reported from the eastern and north-eastern part of the country.[4] Its mold form grows in soil contaminated by bird droppings. People get infected by inhaling microconidia. Human to human transmission do not occur.[5] Our patient came from Kokrajhar Assam.

PATHOPHYSIOLOGY

Inhaled spores of histoplasma capsulatum are phagocytosed by alveolar macrophages, but are not destroyed and multiply in side the macrophages till they split up. The yeast material is taken up by dendritic cells and presented to T cells. CD4+ Th cells produce cytokines which produce oxidative burst in macrophages, Humoral immunity develops with in 10-12 days and clears the infection.[6,7]

In HIV infected patients the disseminated histoplasmosis occurs because of collapse of cell mediated immunity.[8]

Disseminated histoplasmosis usually develops in immunocompromised patients, specially in HIV positive patients. It is characterized by multiorgan damage, especially in the reticulo-endothelial system. Mortality in severe forms of disseminated histoplasmosis is 50-70 %.[9]

LABORATORY DIAGNOSIS

Microscopy is simple, rapid, and cheap but have less than 50% sensitivity. Bronchoalveolar lavage, tissue biopsies, peripheral blood, or bone marrow aspiration are the unseal samples for microscopy. May-Grünwald Giemsa stained smears are examined for yeasts inside macrophages. Small yeast cells (2–4 μm in length) are usually ovoid with budding on a narrow base at the smaller end. Some times extracellular yeast in clusters can be also seen. In Giemsa-stained preparations, a pale blue ring (the fungus cell wall) surrounds the darker blue cytoplasm that retracts from the wall, often giving the false impression of a capsule; the chromatin stains dark violet and appears as a crescent-shaped mass within the cell (Figures 2 and 3). Other stains that can be used are H&E, GMS, PAS.

Gold standard for diagnosis is culture in blood agar or Brain–heart infusion agar with cystein or Sabouraud's dextrose agar medium. But culture is time consuming taking up to 6 weeks.[10]

Other tests employed for diagnosis are Antigen detection by enzyme immunoassays (EIA), PCR, specific antibody detection. [5]

DIFFERENTIAL DIAGNOSIS

Most important differential diagnosis in HIV-infected individuals is miliary tuberculosis (TB), disseminated cryptococcosis, visceral leishmaniasis, and lymphoma ,Penicillium marneffei.[11]

Histoplasmosis continues to frequently be confused with tuberculosis. Culture tests and other focused investigations are required to support the tuberculosis diagnosis. Also, before contemplating multidrug resistant tuberculosis in patients who do not respond well to antituberculosis therapy, doctors must rule out histoplasmosis, particularly in AIDS patients.[12]

Coccidiomycosis, Para coccidioidomycosis, and blastomycosis are a few more deep mycoses that require differential diagnosis. Because the inoculum enters the host through the respiratory system, all of these mycoses have a similar etiology. All of these have the potential to result in lesions of the lungs that resemble TB. They vary, however, in terms of morphology and epidemiology.[10]

TREATMENT

Liposomal Amphotericin B is the treatment of choice, other option is Itraconazole. [5]

CONCLUSION

In our case the presence of pancytopenia prompted clinicians to request for a bone marrow study which revealed intracellular parasitic yeast forms. The diagnosis of histoplasmosis should be considered in immunocompromised patients with sputum negative TB specially in endemic areas like Assam. Mortality in immunocompromised patients with disseminated histoplasmosis remains high. Early diagnosis and prompt treatment will lead to decreased mortality.

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