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Case Series

Pathology Section

Incidentally Diagnosed Disseminated Histoplasmosis among Non HIV Patients: A Series of Three Cases with Review of Literature

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ABSTRACT

Histoplasmosis is a rare airborne fungal infection that is soil-based and is mostly documented in Human Immunodeficiency Virus (HIV)-positive patients. It is common in people living near valley regions. Hereby, authors report three cases of Asian women from different regions of Southern Rajasthan who died due to delayed diagnosis of histoplasmosis within a few days of admission. They all had complaints of fatigue and fever for one month. One presented with decreased urine output and pancytopenia, while the others had complaints of prolonged fever with pancytopenia and fatigue. In all three cases, bone marrow examination was done, and they shared the same diagnosis - disseminated histoplasmosis. It was further confirmed by special stains and microbiological investigations. Authors also reviewed recent articles based on South Asian region histoplasmosis case reports and found three case presentations with the same clinical presentation and outcomes. Treatment was started, but patients deteriorated and died within 10 days of admission. Delay in the diagnosis of histoplasmosis leads to the death of patients. Therefore, histoplasmosis should be considered as a differential diagnosis for prolonged fever with pancytopenia and chronic infections.

Keywords: Bone marrow, Diabetes, Pancytopenia, Special stains

INTRODUCTION

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum*. It has two types- *Histoplasma capsulatum* var. *capsulatum* and *Histoplasma capsulatum* var. *duboisii*, which can cause disease in humans [1]. Histoplasmosis is defined according to the European Organisation for Research and Treatment of Cancer/ Mycosis Study Group (EORTC/MSG) in 2008 [2]. It is a disease in which *Histoplasma* species are found positive in any culture or confirmed by histopathology of blood, bone marrow, or any other infected sites. If a patient shows involvement at a single site and lacks symptoms or signs of systemic involvement, the disease is defined as focal histoplasmosis. To decrease the mortality rate due to histoplasmosis, early diagnosis of the disease should be conducted. Most infected individuals remain asymptomatic and do not get diagnosed with histoplasmosis, leading to fatal outcomes. Disseminated histoplasmosis is commonly observed in older and HIV-positive patients [3-5]. Disseminated histoplasmosis is a diseased state where *Histoplasma capsulatum* is present in the blood and bone marrow or the fungus is confirmed from multiple normal sites in the organism [6-8]. It is a common opportunistic infection in HIV-positive patients [9,10]. The time course of the infection in these patients is typically months, but if left untreated, it can be fatal. Authors hereby present three cases of Pyrexia of Unknown Origin (PUO) in 40-45-year-old females with common complaints of fatigue and pancytopenia residing in Southern Asia regions of India.

CASE SERIES

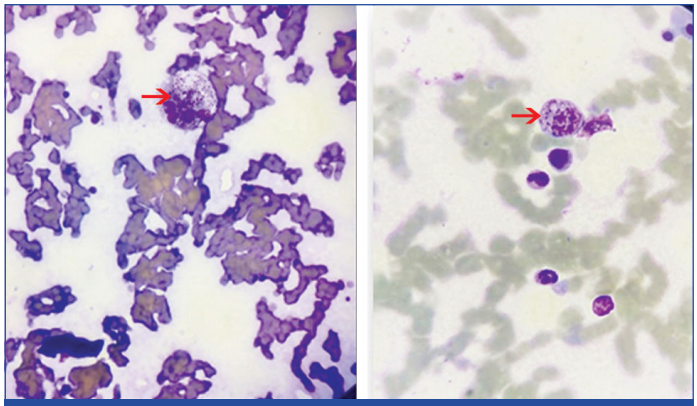
Case 1

A 42-year-old female with a past medical history of Diabetes Mellitus type II and Hypertension for seven years was admitted to the hospital with complaints of decreased urine output, fatigue, diminished vision, and pedal swelling for 10 days. The patient had been on Insulin and other hypertensive medications for the last five years. She had a history of a single blood transfusion 17 days prior at a small centre due to weakness and shortness of breath, where 350 mL of whole blood was transfused. On physical examination, the patient appeared pale, had bilateral pedal swelling, an increased respiratory rate of 35, blood sugar level of 320 mg/dL, and blood pressure of 160/90 mmHg. Diabetic retinopathy was observed on ocular examination. Laboratory investigations from a complete blood count report revealed pancytopenia with a haemoglobin level of 5.8 g/dL, platelet count of 70,000/cumm, and total leukocyte count of 2000/cumm. Urine output was decreased and showed proteinuria with pus cells. Kidney function tests showed derangement with increased urea and creatinine levels of 270 mg/dL and 7 mg/dL, respectively. Liver function tests were normal, and other parameters were within normal limits. A chest X-ray showed normal findings, while an abdominal ultrasound revealed contracted kidneys with mild hepatosplenomegaly, which progressed to moderate splenomegaly in a repeat ultrasound done after three days.

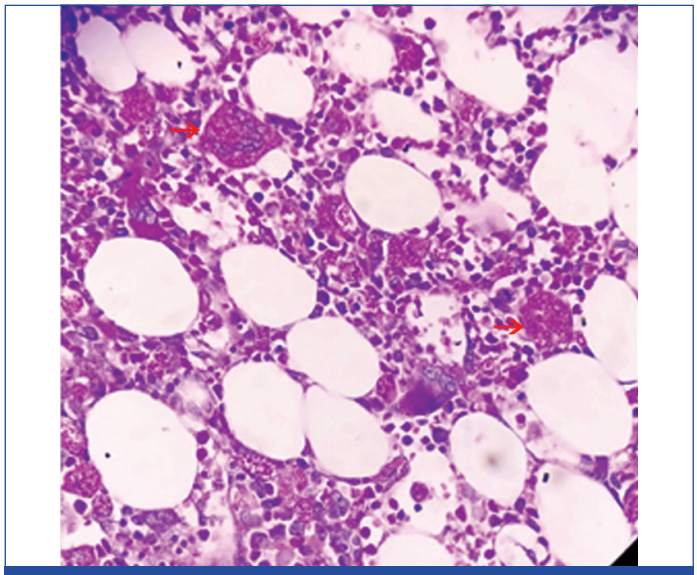
In the following days, the patient started experiencing shortness of breath and altered sensorium. Cerebrospinal fluid (CSF) analysis was performed, and it was normal. Peripheral smear showed morphologically normal findings with pancytopenia. Subsequently, a bone marrow examination was conducted, which revealed small budding intracellular yeast colonies exhibiting a “halo” effect around each organism and haematoxylinophilic nuclei stained with Haematoxylin and Eosin (H&E) stain. Periodic Acid Sciff (PAS) and Grocott-Gomori’s Methenamine Silver (GMS) stains were performed on bone marrow biopsy slides, showing positive intracellular colonies, confirming the presence of *Histoplasma capsulatum* in the bone marrow [Table/Fig-1-3]. Therefore, the diagnosis of bone marrow infiltration by *Histoplasma* was established based on both aspiration and bone marrow biopsy. The patient underwent dialysis, and her creatinine levels improved, but her condition deteriorated, and she passed away within 10 days.

Case 2

A case of 69-year-old female who presented to the medicine Outpatient Department (OPD) with complaints of prolonged fever,



[Table/Fig-1,2]: H&E stain showing intracellular bodies (arrow) in macrophages at 40x and 100x . (Images from left to right)



[Table/Fig-3]: PAS positive histoplasma (arrow) at 40x.

shortness of breath, and fatigue lasting for one month. She was immunocompetent and did not had any other underlying illnesses such as HIV, diabetes, or hypertension. Upon examination and investigation, she was found to be pale, with an elevated respiratory rate. Her blood pressure and pulse were normal. The Complete Blood Count (CBC) report revealed pancytopenia with a haemoglobin level of 10 mg/dL, platelet count of 14,000/cumm, and total leukocyte count of 3000/cumm. Random blood sugar was 273 mg/dL, Lactate Dehydrogenase (LDH) was elevated to 200 U/L, and Dengue NS1 antigen was positive. All other parameters were within normal limits. Kidney function tests, liver function tests, procalcitonin levels, and urine examination were normal. Bone marrow aspiration and biopsy were performed due to pancytopenia, and both tests were positive for intracellular fungal elements in macrophages, confirming histoplasmosis.

On radiological investigations, the chest X-ray showed normal findings, while the ultrasound of the whole abdomen was unremarkable. A Computed Tomography (CT) scan of the brain revealed mild periventricular hyperdensity in the right parietal regions, possibly indicating soft calcifications. The patient was transferred to the Respiratory Intensive Care Unit (ICU) within two days, and her condition continued to deteriorate, and passed away within 10 days of admission. Meanwhile, she was being treated for dengue with steroids and fluid infusion as symptomatic treatment.

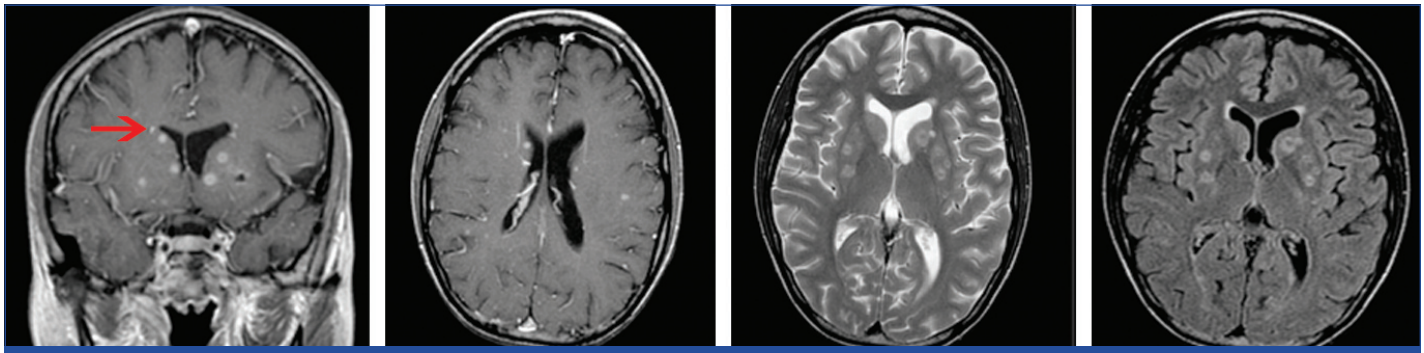
Case 3

Another case was reported during the same period at Jodhpur Government Hospital. A 48-year-old female presented with breathlessness, fever, and fatigue and was admitted to the ICU. All investigations were conducted, and the CBC revealed pancytopenia, along with an elevated LDH level of up to 300 IU/L. Her chest X-ray showed diffuse areas of involvement, but all other investigations were normal. She had a brief history of cough and breathlessness. Steroids were initiated to address the shortness of breath, but no improvement was observed.

On bone marrow examination, small budding intracellular yeast colonies were identified, displaying a “halo” effect around each organism and haematoxylinophilic nuclei stained with H&E stain. PAS and GMS stains were performed on bone marrow biopsy slides, showing positive intracellular colonies confirming the presence of *Histoplasma capsulatum* in the bone marrow, with the same morphology as the identified histoplasma. Subsequently, the patient developed seizures, prompting a suggested Magnetic Resonance Imaging (MRI) of the brain, the findings of which are explained below [Table/Fig-4-7]. Antifungal therapy was initiated, resulting in an improvement in the CBC, but unfortunately, the patient passed away within two days. Once again, a delay in diagnosis and hesitation to administer antifungal therapy contributed to the patient’s death.

DISCUSSION

Three cases of histoplasmosis were reported in apparently immunocompetent individuals from the desert and arid zone in western Rajasthan, India. The patients presented with similar complaints of pancytopenia and weakness. None of them were initially diagnosed with disseminated histoplasmosis. Humans acquire this infection through the inhalation of microconidia of yeast. Most infected individuals also experience haematogenous spread of the organism to reticuloendothelial organs such as the liver, spleen, and bone marrow [4]. A review study conducted in South Asia by Wang TL et al., on disseminated histoplasmosis noted that none of the reports initially considered histoplasmosis in the early diagnosis [11]. First case was initially considered chronic kidney disease as the cause of bone marrow suppression leading to pancytopenia. Dialysis was performed, her renal status improved, but her clinical condition did not. She developed altered sensorium, breathlessness, anorexia, and her oxygen levels dropped. Subsequently, along with dialysis, her bone marrow work-up was initiated. On bone marrow examination, aspiration revealed the presence of intracellular yeast colonies with a “halo”



[Table/Fig-4-7]: MRI images shows multiple tiny 2 flair hyperintense lesion (arrow) 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 oedema. (Images from left to right).

effect inside macrophages, shown in [Table/Fig-1,2] known as the Haemophagocytosis phenomenon [12]. The bone marrow biopsy showed fungal filaments, although histoplasmosis can be confused with *Cryptococcus* and *Blastomyces dermatitidis*, they can be differentiated based on the fact that cryptococci are carminophilic and *Blastomyces* cells are multinucleated, thick-walled, and bud from a base. The most important distinguishing feature is that only *Histoplasma* is PAS and GMS positive, as shown in [Table/Fig-3], while other fungi show a negative response to these special stains.

In first case, patient had a history of previous blood transfusions and i.v. iron transfusions at some small centre. When the diagnosis was made, liposomal Amphotericin B was advised to the patient, but unfortunately, the patient died. It is worth noting that the lungs remained normal until the end, and the infection spread rapidly throughout all tissues. Within 10 days of admission, the patient passed away. She developed moderate hepatosplenomegaly towards the end. If the diagnosis could have been made earlier, the patient might have been saved. Therefore, Histoplasmosis should be considered in the differential diagnosis among patients with chronic kidney disease along with any immunocompromised conditions [13]. In India, the disease is endemic in the eastern part, with most cases reported in the Gangetic West Bengal [14]. Other two patients also presented with the same complaints of fever and pancytopenia and were diagnosed with disseminated histoplasmosis.

Samaddar A and Sharma A concluded that diagnosing disseminated histoplasmosis at an early stage is very challenging due to its common symptoms, which are similar to other infectious diseases, especially in immunocompetent individuals, similar to present study [15]. The fact that patients who do not visit endemic areas are contracting the disease is a point of concern, indicating that the western arid region of the Indian subcontinent is also becoming endemic to this disease. In another study by Kathuria S et al., it was reported that adrenal glands were the most commonly involved organs in disseminated histoplasmosis, followed by the liver, skin, spleen, lymph nodes, and bone marrow [16]. Wang N et al., demonstrated that disseminated histoplasmosis infection can present with unexplained fever, and that metagenomics Next generation Sequencing (mNGS) can be a valuable complement to bone marrow aspiration for diagnosing this disease, similar to index cases presenting with PUO [17]. Therefore, PUO should definitely be evaluated for histoplasmosis in arid regions as well.

CONCLUSION(S)

Patients with *Histoplasma* infection are predominantly women. There are no defined age and immune status criteria for this deadly infection. Therefore, patients presenting with prolonged fever and pancytopenia should be evaluated for *Histoplasma* infection regardless of the rarity and immune status of those affected. In all three cases of the above cases, the medical community failed to save the patients due to delayed diagnosis. Based on the epidemiological data of histoplasmosis in nearby valley regions, these cases challenge the notion that this infection is limited to humid areas, as they were reported in dry regions during the months of November to January. Disseminated histoplasmosis should be considered as a differential diagnosis in patients with chronic kidney disease presenting with pancytopenia and should be treated promptly to improve outcomes. This deadly disease does not discriminate based on age or timing of onset. Over the past few years, cases of disseminated histoplasmosis have been rapidly reported worldwide, despite endemic and geographical variations. However, more systematic and comprehensive studies are needed in this field to accurately estimate the true burden of histoplasmosis.

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