Case Report

Progressive disseminated histoplasmosis in idiopathic CD4 lymphocytopenia an underdiagnosed combination - a case report

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Abstract

Progressive disseminated histoplasmosis (PDH) usually presents as fever, anemia, leukopenia, hepatosplenomegaly, lymphadenopathy and pulmonary symptoms. There are few reports on the association of idiopathic CD4 lymphocytopenia (ICL) with histoplasmosis. We describe a 65-year-old female presented with a history of fever, papulo-nodular rash and significant weight loss and diagnosed as progressive disseminated histoplasmosis. All immunocompromised conditions were ruled out. In addition, her 2 consecutive CD4 counts were below 300. The patient was diagnosed with PDH associated with ICL. The patient showed significant improvement with liposomal amphotericin B and itraconazole. Absolute CD4 counts should be done in all cases of progressive disseminated histoplasmosis even in HIV negative individuals to rule out associated ICL.

Keywords: progressive disseminated histoplasmosis, idiopathic CD4 lymphocytopenia, immunocompromised individuals, HIV negative individuals

Introduction

Histoplasmosis is an opportunistic systemic fungal infection caused by dimorphic fungi, *Histoplasma capsulatum*. It involves cells of the reticuloendothelial system and has a varied clinical spectrum ranging from acute pulmonary histoplasmosis to progressive disseminated histoplasmosis [1]. Progressive disseminated histoplasmosis (PDH) occurs in 10% of the cases and usually presents as fever, anemia, leukopenia, hepatosplenomegaly, lymphadenopathy and pulmonary symptoms [1]. Only a few cases have been reported from the arid zones of North India. In India, it is usually found on the riverbanks of Ganga and Brahmaputra. This may be due to the use of nitrogen and phosphorus rich organic fertilizers and bats manure [2]. Progressive disseminated disease is seen in the immunocompromised individuals, most commonly with HIV/AIDS. However, it is rarely reported with immunodeficiency diseases like idiopathic CD4 lymphocytopenia (ICL) and common variable immunodeficiency (CVID) [3]. We diagnosed an unusual case of PDH in the arid zone after ruling out the common immunodeficiency states. Further investigations elucidated a rare association with idiopathic CD4 lymphocytopenia.

Case presentation

A 65-year-old female, from a small desert village in western Rajasthan, presented to emergency department (day 0) with complaints of fever and papulo-nodular rash all over the body for two months (Figure 1A), dry cough and gradually progressive breathlessness on walking for 15 days.

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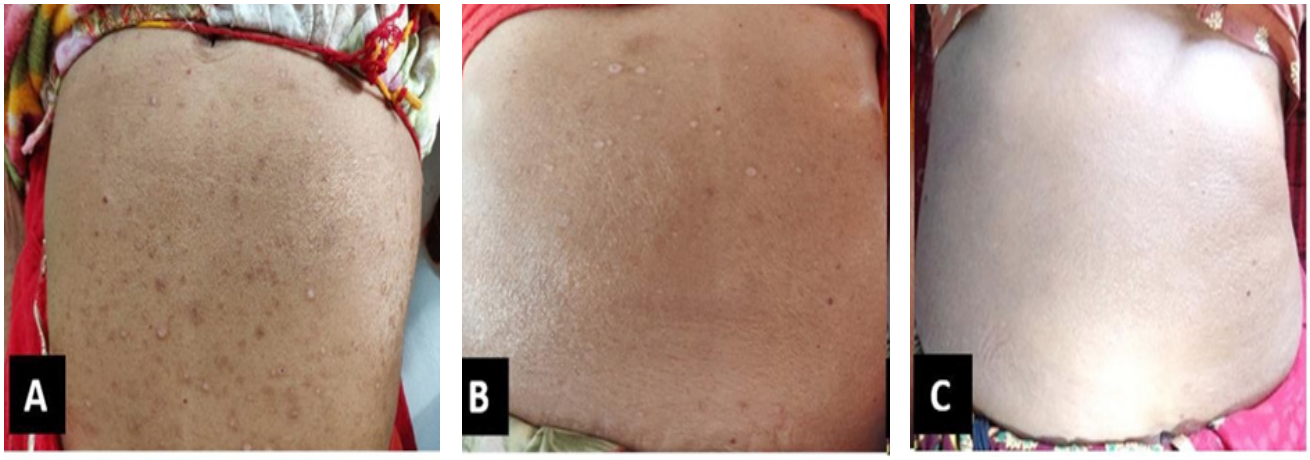

Figure 1A: Papulo-nodular rashes over anterior abdominal wall (Day 0), **Figure 1B:** Resolution of rashes after two weeks of Injectable Liposomal Amphotericin B (Day +24), **Figure 1C:** Complete resolution of rashes after 3 months (Day +100)

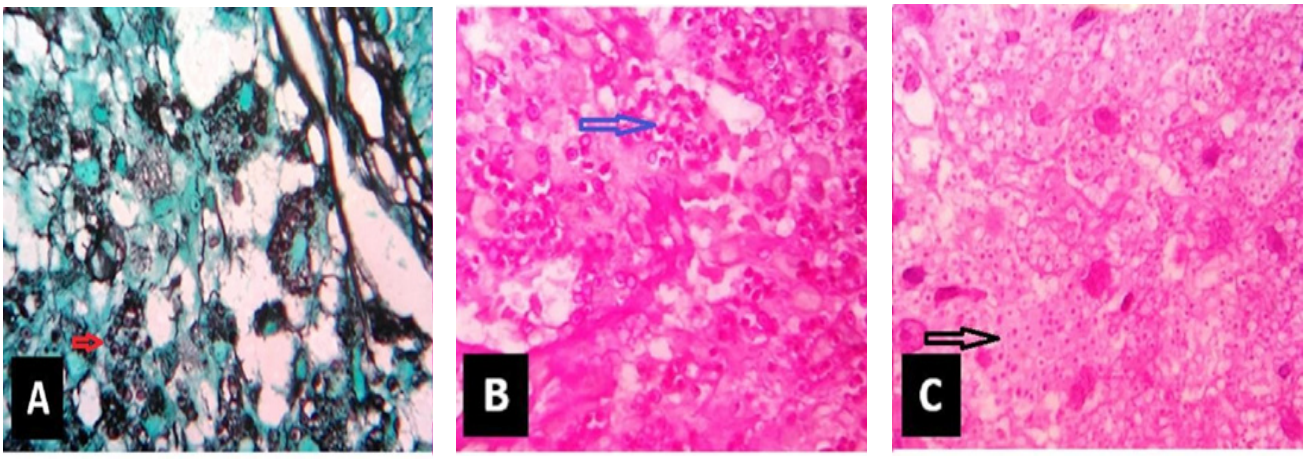

Figure 2A, 2B, 2C (Day +7) - Skin biopsy revealing macrophages with similar intracellular yeast forms highlighted with Gomori methenamine silver (GMS) stain, periodic acid schiff (PAS) stain and Hematoxylin and eosin stain (H & E stain) (A. GMS, B. PAS, C. H & E), arrow shows infected cells.

She also complained of significant weight loss and decreased appetite. She gave the history of contact with the case of varicella infection in her family and after 10 days of contact she developed the illness. She received treatment for varicella infection (Valacyclovir) at the primary health centre but did not improve. There was no other significant past medical or surgical history. The patient had no history of travel outside her locality in recent past. On physical examination, she had multiple papulo-nodular lesions with adherent crusting that were present over the abdomen, neck, back, and thigh. Bibasilar crepitations in the lung along with significant hepato-splenomegaly were detected on systemic examination.

On laboratory investigations, pancytopenia was present in complete blood count (Hb: 7.1 g/dl, total Leucocyte count: 3850/micro L, platelet count: 42000/micro L) and peripheral smear showed occasional macrocytes without immature cells. Erythrocyte sedimentation rate was 65 mm/1st hour and High-sensitivity C-reactive protein was 83.21 mg/dL. In liver function test, serum bilirubin was 0.69 mg/dl, aspartate aminotransferase was 0.27 micromol/L, alanine transaminase was 0.63 micromol/L and total proteins were only 4.17 gm/dL with serum albumin of 1.83 gm/dL. The kidney function test was normal and viral markers (HbsAg, Anti HCV and HIV) were negative. Chest X-ray was unremarkable except prominent bronchovesicular markings. Her random blood glucose level was 102 mg/dl, HbA1c was 36.6 mmol/mol. Antinuclear antibody test (ANA) was negative.

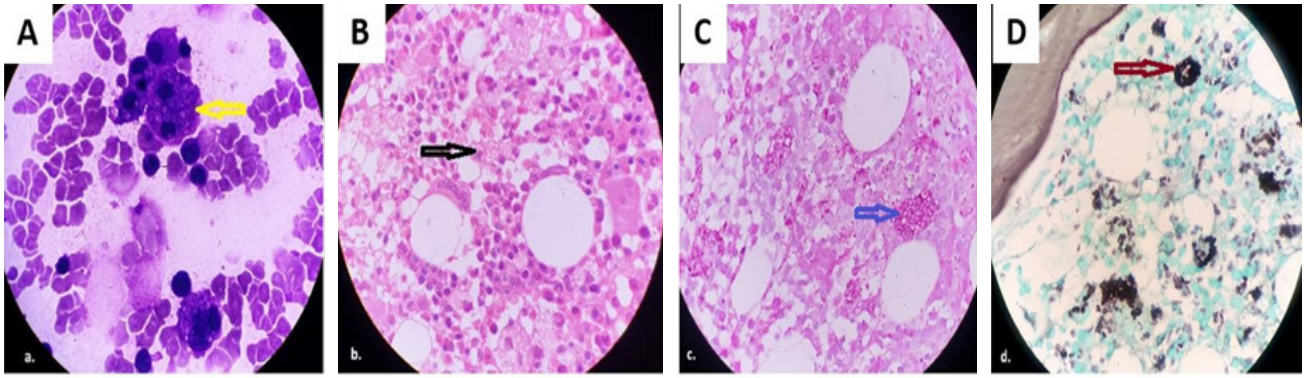

Figure 3A (Day +10) Bone marrow aspirate smear revealing macrophages with intracellular yeast forms consistent with Histoplasma capsulatum (Giemsa, 100X); arrow shows the yeast forms. **Figure 3B, 3C, 3D.** Bone marrow biopsy revealing macrophages with similar intracellular yeast forms highlighted with periodic acid schiff (PAS) stain and Gomori methenamine silver (GMS) stain (B - H&E).

Skin biopsy was done from papulo-nodular lesions and smears were stained with Toluidine blue (on-site), Giemsa, and Papanicolaou (PAP) stains (Day +7). The sections showed fragmented tissue lined by stratified squamous epithelium with focal surface exudation. Sub-epithelium showed multiple ill-formed epithelioid cell granulomas along with scattered small cells having eosinophilic nuclei with perinuclear halo engulfed by foamy macrophages. Dense inflammatory infiltrates comprising of plasma cells, lymphocytes, giant cells, and mast cells were present. Differential diagnosis of *Histoplasma capsulatum, cryptococci* and *Leishmania donovani* were kept. Periodic Acid Schiff and Gomori methenamine silver (GMS) stain were positive in the small cells engulfed by macrophages, these were negative for mucicarmine, consistent with *Histoplasma capsulatum* (Figure 2A, 2B, 2C).

Ziehl Neelsen (ZN) stain was also negative and there was no evidence of dysplasia. Bone marrow aspiration and biopsy were also consistent with Histoplasma capsulatum (Figure 3A, 3B, 3C, Day +10).

Mycology culture from cutaneous lesions and the bone marrow aspirate were performed, which were negative. The diagnosis of progressive disseminated histoplasmosis was kept. We have also ruled out the common immunocompromised conditions. Her immunoglobulins (IgG, IgA, IgM) and complement levels were within normal limit. HIV 1/2 and other viral infections (Hepatitis B, C, EBV, CMV, Human Herpes virus-6) that can cause CD 4 cell lymphopenia were also ruled out. We went for CD4 counts which came only 53 /micro L and 250 /micro L on two occasions three months apart, and the diagnosis of idiopathic CD4 lymphocytopenia was made. She was treated with injectable liposomal Amphotericin B in the dosage of 150 mg per day (3 mg/kg/day) for two weeks with significant clinical improvement (Figure 1B at Day +24, 1C at Day +100). The patient was discharged on oral Itraconazole 200 mg twice daily (to be continue for next 12 months). She is on regular follow up since the last seven months and is currently asymptomatic.

Discussion

Samuel Darling first described *Histoplasma capsulatum* in 1906 while investigating a case of miliary tuberculosis. The name *Histoplasma capsulatum* was coined as it appeared as an encapsulated organism in histiocyte [4]. In India, the first case of histoplasmosis was diagnosed in 1954 by Panja and Sen from Kolkata [5]. Histoplasmosis is endemic in north east, West Bengal and Uttar Pradesh region of India due to their temperate climate and organic nitrogen rich soil [2]. Very few cases were reported from the non-endemic region of India like Rajasthan. Patel et al. reported 7 cases of histoplasmosis from Rajasthan [6]. We report this case from the hot and dry climate area of the Western India. There are secluded areas in villages of Rajasthan, frequently visited by birds and bats. Moreover, the increase in constructional activities in these areas also increases the chances of contact between human and bird manure, which eventually increases the risk of histoplasmosis. Liver, spleen and bone marrow involvement are present in more than two-third patients with histoplasmosis [2]. Our patient had fever, pulmonary symptoms, cutaneous lesion, hepatosplenomegaly and pancytopenia. Pulmonary involvement is present in up to 90% of cases and the most common chest X-ray finding is prominent bronchovesicular markings as seen in our case [7]. The clinical presentation of pulmonary and disseminated histoplasmosis can be easily confused with tuberculosis, sarcoidosis, malignancy and other fungal infections (Aspergillosis, Blastomycosis). This case was also treated as a varicella infection initially but not improved and subsequently diagnosed as disseminated histoplasmosis. *Histoplasma capsulatum* is a dimorphic fungus which grows as a mycelial form in soils

and yeast form in host cells. The inhalation of mycelium with microconidia (spores) into lungs is the portal of entry in humans. This is an intracellular micro-organism and multiplies as yeast form in macrophages of lung parenchyma and widely spreads in reticuloendothelial tissues [8]. The specific cell-mediated immunity against *Histoplasma*, which develops in one to three weeks of infection, leads to the recovery from the disease [9]. Defective cell-mediated immunity is associated with progressive dissemination of fungi like in HIV/AIDS, patients on immunosuppressive therapy, ICL, and chronic granulomatous disease. In India, a total of 388 cases of histoplasmosis were reported from 1995 to 2018, highest number of cases were from West Bengal and Uttar Pradesh. The majority of cases were diagnosed on the basis of histopathological characteristic of yeast form of *Histoplasma capsulatum* [1]. The most common underlying immunodeficiency disease associated with these cases was HIV/AIDS (around 70%) [2,10]. Other underlying immunodeficiency diseases were: renal transplant recipients, malignancies and oral steroids. Immunodeficiency syndromes like Job syndrome and ICL were seen in very few cases [2,10]. This may be partly due to a lack of awareness about these disorders among clinicians.

Our patient had CD4 counts of only 53 /µL and 250/ µL on two occasions, 3 months apart and HIV 1 and 2 were negative suggesting the diagnosis of idiopathic CD4 lymphocytopenia [11]. Two similar cases of idiopathic CD4 lymphocytopenia with disseminated histoplasmosis were also reported from India [12,13]. The diagnostic criteria of this condition are absolute CD4 T lymphocyte count <300/µl or <20% of total T cells on two occasions in the absence of HIV 1 and 2 infection and other immunosuppressive conditions [11]. A total of 258 cases were diagnosed with ICL in 143 published papers in literature till 2013 [14]. Regent et al. found cryptococcal infection (26.7%) as the most common opportunistic infection followed by mycobacterial infection (17%) and histoplasmosis (3.1%) in ICL [14]. Subsequently, around 66 more cases were reported till 2020 in the literature [15]. Among them, a cases series of 40 patients showed that opportunistic infections were present in 62.5% of ICL cases (human papilloma virus, cryptococcus meningitis, pneumocystis pneumonia and mycobacterial tuberculosis were most common infections) [15]. The association of histoplasmosis and ICL is rare and CD4 count was not done in all reported immunocompetent cases. We suggest that CD4 count should be done in all cases of histoplasmosis after ruling out common immunodeficiency states like HIV/AIDS. The common risk for exposure to *Histoplasma capsulatum* is farming or agriculture-related, exposure to birds, construction workers, woodcutter, grain factory workers, forest officers and exposure to chicken coops [2]. The high inoculation of mycelia is occasionally associated with disseminated histoplasmosis in immunocompetent persons. There was a history of construction work in the vicinity of the patient's house for last one year. With an increase in the expertise in clinical and laboratory services, the detection of disseminated histoplasmosis has risen even in non-endemic areas of the world. The definitive diagnosis of histoplasmosis requires the demonstration of fungi in histopathology, cytopathology, or cultures. Histopathological characteristic from skin biopsy has good sensitivity and a rapid and cost-effective way of providing a presumptive or definitive diagnosis of disseminated histoplasmosis [1]. The histopathological characteristic is very helpful in differentiating between the fungi as, broad-based budding yeasts (10–15 µm) seen in Blastomyces dermatitidis, narrow-based budding yeasts (4–10 µm) with a thick capsule positive for mucicarmine and Fontana-Masson seen in *Cryptococcus*. Small yeasts (2–4 µm) with narrow-based budding grouped in clusters inside macrophages and positive for PAS and GMS is suggestive of *Histoplasma capsulatum*, *Coccidioides immitis*/*posadasii* has spherules with multiple endospores, and small yeasts (3–5 µm) intermingled with pseudohyphae and/or hyphae pointed towards *Candida* [16]. Culture is the most definitive for diagnosis but it takes around six weeks for the organism to grow and delays the diagnosis. The maximum yield of culture is from bone marrow or blood. The present case was diagnosed based on histopathological features, though cultures from skin and bone marrow showed no growth. Histopathology and culture mismatch might be due to either aggressive pulverization of fungal cells leading to destruction or fungal cell not viable in culture sample [17]. Antigen detection in blood and urine and serum antibody detection are useful tests in the diagnosis of acute histoplasmosis, but not easily available in India. Molecular diagnosis of *Histoplasma* from biopsy tissue is an important addition for culture negative cases, however, this requires technical expertise and is not widely available. Acute pulmonary histoplasmosis and progressive disseminated histoplasmosis should be treated with injectable Amphotericin B for two weeks followed by oral Itraconazole [1]. Our patient responded well with injectable amphotericin B and now on oral Itraconazole with continuous clinical improvement.

Conclusion

Progressive disseminated histoplasmosis is an opportunistic infection and though rare should be suspected especially in fertile areas and near construction sites. It warrants an extensive workup to rule out underlying immunodeficiency state. The clinician must evaluate for CD4 cell counts in all cases of progressive disseminated histoplasmosis even in HIV negative individuals to rule out idiopathic CD4 lymphocytopenia.

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