Case Report

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# A Rare Primary Mucocutaneous Presentation of Chronic Disseminated Histoplasmosis in an Immunocompetent Young Female: A Case Report

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## Abstract

Classical Histoplasmosis also known as Darling's disease is a systemic mycosis caused by dimorphic fungus, Histoplasma capsulatum var capsulatum and Histoplasma capsulatum var duboisii. It is an opportunistic fungal infection that usually affects immunocompromised patients. Though microbiology culture methods are the gold standard, scrape cytology and histopathology give a relatively rapid diagnosis. It may pose a diagnostic dilemma on histopathology and morphology needs to be carefully studied to rule out other differentials. We present a rare case of chronic disseminated histoplasmosis with primary mucocutaneous lesions in an immunocompetent young female patient. This study is ethically approved from the institute and due written consent for publication from the patient has been taken.

***Keywords***: *Disseminated, histoplasmosis, immunocompetent, mucocutaneous*

## Introduction

Classical Histoplasmosis also known as Darling's disease [1] is a systemic mycosis caused by dimorphic fungus, Histoplasma capsulatum var capsulatum and Histoplasma capsulatum var duboisii. It is an opportunistic fungal infection caused by inhalation of the microconidia (the mold form) of Histoplasma. They are found in soil and bird droppings. [2,3] The species Histoplasma capsulatum is endemic in America particularly the Ohio and the Mississippi river valleys of North America, [4,5] whereas Histoplasma duboisii is endemic in Africa. [6] In India, endemic cases of histoplasmosis have been reported in West Bengal (eastern India), especially along the Gangetic delta. [4,5,7] Sporadic cases have been reported in southern India. [8,9] Reports of histoplasmosis from nonendemic regions is very rare.[10] Histoplasmosis can occur in three forms: (i) Primary acute pulmonary form (ii) chronic pulmonary and (iii) disseminated form.[11,12] Disseminated disease usually occurs in immunocompromised patients or in patients with chronic illness. [13] However there are few case reports of this disease in immunocompetent patients as well. [14,15] Histoplasmosis is traditionally and directly diagnosed by histopathology using specific stains, as well as by isolation of the fungus in culture, which is considered as the gold standard. [16] Culture may take 4 weeks whereas scrape cytology and biopsy is a rapid method of diagnosis and helps to start treatment earlier. We report a rare case of disseminated histoplasmosis in an immunocompetent patient of a non-endemic region of India.

## Case Report

A 23-year-old female, housewife and resident of Shardul district, Madhya Pradesh (Central India) presented with multiple erythematous papules over face, chest, back, bilateral upper limbs and lower limbs for 4-5 years. ( Figure 1) These patches were initially white and were first noticed on bilateral arms. After 9-10 months she started developing erythematous non tender, non-painful papules over entire body. The lesions were misdiagnosed in a private setup as a leprosy case and was started on anti – leprosy treatment (MBMDT) for leprosy however lesions did not completely resolve. She also had red to white papular ulcerated lesions in oral cavity since three years. Patient was on homeopathic treatment for 2 yrs for the same. Lesions flared up over three months and she came to our institute. We received skin biopsy, oral cavity lesion scrapings and bone marrow trephine biopsy. (Fig 2,3,4,5,6).

We received a skin biopsy which was followed by cytology and bone marrow samples. On examination, the lesions were erythematous & papular and appeared coalescing at places. Also seen was pus discharge and crusting. A scrape cytology was performed on oral cavity and cutaneous lesions. A chest X-ray and a chest PET scan done, revealed no significant abnormality. Patient was negative for human

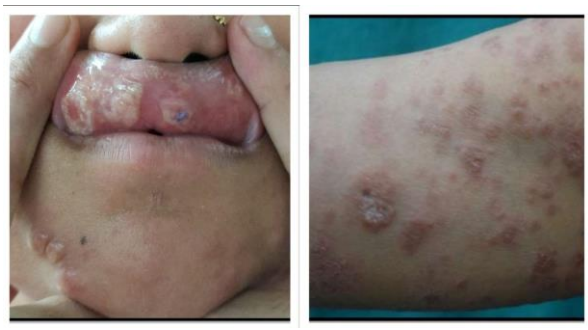

***Figure 1: Multiple erythematous papules in oral cavity and face and over arm.***

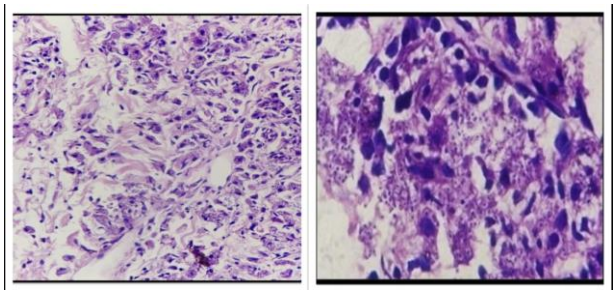

***Figure 2: 400 X and 1000X H&E: The dermis, epidermo - dermal junction shows presence of multiple granulomas comprising of histiocytes, lymphocytes and plasma cells. Many macrophages are infested with numerous H.Capsulatum organisms.***

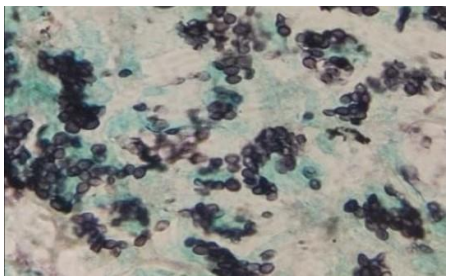

***Figure 3: 400 X Special stain Gomori Methamine Silver positive H. capsulatum***

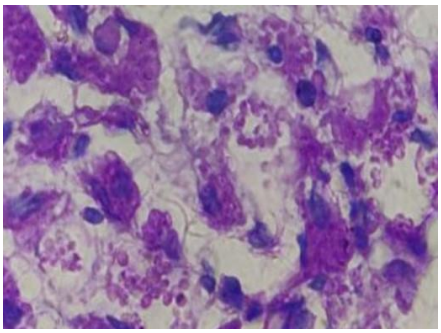

***Figure 4: 400 X Special stain Periodic acid Schiff stain positive H. capsulatum***

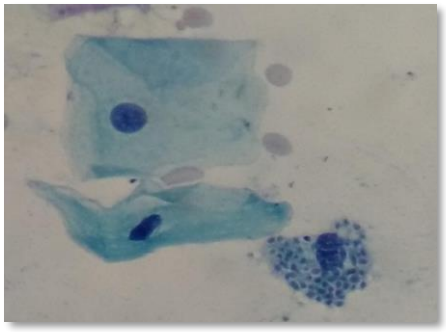

***Figure 5: 400 X Papinocoloau stain Oral cavity lesion scrapings showing macrophage infested by H. capsulatum.***

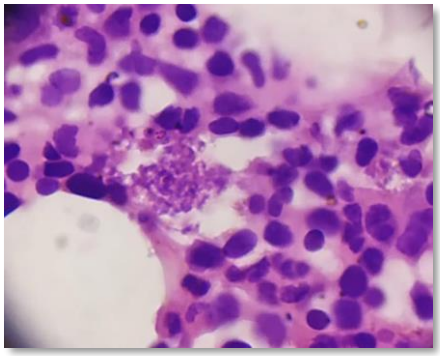

***Figure 6: 400X H&E Bone marrow biopsy showing macrophages infested with H. capsulatum.***

immunodeficiency virus (HIV), hepatits C and hepatitis B. Her hemoglobin level was 9 gm/dL, total leukocyte count was 13,000/ mm3, platelet count was 3.2 lakhs/mm3 and peripheral smear showed normocytic normochromic anemia. CD 4 count- 432 (Normal- 500-1,500); CD 4 % - 42% (Normal range- 25% -65%). Chest X ray & Chest CT/PET scan showed no pulmonary lesions. Erythrocyte sedimentation rate (ESR) level was 40 mm/1st hour. Liver Function Tests (LFT), Renal function tests (RFT) and random glucose levels were within normal limits.

The H & E of skin biopsy showed presence of multiple epithelioid granulomas composed of multinucleated giant cells and many macrophages stuffed with numerous yeast form organisms. Few were present extracellulary as well. Special stains Gomori Methamine Silver (GMS), Periodic Acid Schiff (PAS), mucicarmine were done keeping in mind differentials of other infectious organisms which were cryptococcus, Blastomyces & LD bodies (leishmania donovani). GMS and PAS were positive. Special stain Fite farraco was done to rule out leprosy as she was treated for it. We observed that the said organism had no rod and kinetoplast and had a definite halo around it, and mucicarmine was negative. Size was smaller and no broad base budding was seen (Figure no.3). Hence a diagnosis of histoplasmosis was given. After few days a scrape cytology was received and a week later a bone marrow aspiration &

biopsy of the same patient was received and similar diagnosis were given in each of them respectively. Hence a final diagnosis of disseminated histoplasmosis was given and was confirmed by culture reports of microbiology as well.

She was then treated with amphotericin B for 2 weeks and currently under maintenance medication of itraconazole and is doing well in 6 months of follow-up.

## Discussion

Disseminated histoplasmosis in an immunocompetent patient is rare. [14,18] In human immunodeficiency virus (HIV) positive patients, 95% of histoplasmosis appears as disseminated infection. Occurrence of disseminated form of histoplasmosis is rare in HIV seronegative patients. [18] In our case patient is immunocompetent (HIV negative) and belongs to a non endemic region of India (Madhya Pradesh). The district Shardul is a forest area with many caves, which are heavily bat infested. It is likely that our patient due to her chronic exposure to bat droppings may have been infected by histoplasma.

Rarity and unusual presentation in immunocompetent patient, often leads to misdiagnosis as happened in this case. Patient was misdiagnosed as having leprosy ( another endemic disease in India) and was also treated for the same. An article by Dibyendu De et al [7] states that it is often misdiagnosed and therefore less no of cases are reported in immunocompetent patients and authors of this study second that. However this study [7] is from an endemic region of India.

The symptoms presented in disseminated histoplasmosis are fever, weakness, weight loss, hepatosplenomegaly, and mucocutaneous lesions. [19] Our patient had similar clinical presentation except for organomegaly. The oral lesions may occur in any part of the oral cavity and the lesions vary from nodules to painful shallow or deep ulcers. [19] The incidence of oral manifestation is 25-45% in the disseminated form of the disease. [20] Our patient initially had cutaneous lesions and later had oral lesions as well. Mucocutaneous presentation of disseminated histoplasmosis is commonly reported in AIDS patients [21] but is rare to find it in an immunocompetent patient. [22] Our patient came for skin biopsy followed by scrape cytology and then bone marrow biopsy. On histopathology, on H& E we thought of intracellular fungal infections and the differentials were Histoplasma capsulatum, cutaneous Leishmaniasis, cryptococcus, cutaneous blastomyces and also erythema nodosum. (Refer Table no. 1).

In present case the GMS & PAS were positive rest all negative which narrowed the diagnosis to Histoplasmosis, leishmaniasis and blastomycosis. Leishmaniasis was ruled out due to absence of rod & kinetoplast. The yeast forms size were 2 – 4 microns with narrow based budding and showed presence of thick cell wall, so blastomycosis was also ruled out. Hence a diagnosis of histoplasmosis was given. Similar findings were noted in scrape cytology, bone marrow aspiration and biopsy. As a result a final diagnosis of disseminated histoplasmosis was given.

***Table 1: Differential diagnosis of Histoplasma on morphology seen in H & E and special stain profile. 11***

| Differential diagnosis considered | H & E | Size | Special stains | | |
|---|---|---|---|---|---|
| | | | GMS & PAS | Mucicarmine | Fite faracco |
| **Histoplasma capsulatum** | Presence of intracellular yeast forms. Have thick refractile cell wall & bud by relatively narrow base. Hourglass/double cell/ figure eight budding forms are created. | 8 -15µm | +/+ | - | - |
| **Cutaneous Leishmaniasis** | Usually intracellular but have a rod and kinetoplast | 5 – 6 | +/+ | - | - |
| **Cryptococcus** | Intracellular and have a halo around it | 2 - 20µm | +/+ | + | - |
| **Blastomycosis** | Intracellular and have a thick wall & a broad base budding is seen. | 20 - 30 µm | +/+ | Weak positivity | - |
| **Erythema odosum leprosum** | Intracellular and macrophages are filled with bacilli but not visible on H & E | Very small | -/- | - | + |

Histopathology is a rapid means of diagnosis of histoplasmosis. According to Santosh T et al [16] scrape cytology is a cost effective and rapid means of diagnosis to start early treatment and we second this. Our patient is a housewife and immunocompetent, with history of exposure to caves and bat droppings. There was no documented/ verbal drug history of steroid and chemotherapy.

## Conclusion

Disseminated histoplasmosis is usually a misdiagnosed disease due to its rarity in a by enlarge non endemic country like India, its unusual presentation and lack of suspicion in immunocompetent patients. Cytology & histopathology are rapid methods of diagnosis compared to gold standard culture method, which may take upto 4 weeks. Scrape cytology is the quickest method & results can be given in 1 - 2 days. Clinician should keep this disease in differentials for pyrexia of unknown origin even in an immunocompetent patient.

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