

Multipronged Diagnostic Modalities Help to Crack a Case of Progressive Disseminated Histoplasmosis Presenting with Ambiguous Dermatological Lesions

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Abstract

Background: Histoplasmosis is a granulomatous fungal disease, caused by *Histoplasma capsulatum*, an intracellular dimorphic fungus, usually found in soil contaminated with bird and bat excreta; transmitted by aerosolized microconidia inhalation. The most common clinical presentation is acute or chronic Pulmonary Histoplasmosis.

Case Presentation: In this case report, a perplexing diagnostic scenario involving a 56-year-old patient who was HIV-negative but had diabetes mellitus and hypertension, in conjunction with unclear dermatological lesions has been presented. Despite treatment, the lesions did not respond favourably, posing a diagnostic dilemma. The identification of yeast forms in skin biopsy indicated progressive disseminated histoplasmosis, a diagnosis validated by PCR analysis, detection of *Histoplasma galactomannan* antigen in urine, and a positive fungal culture. A course of IV Liposomal Amphotericin B followed by oral Itraconazole, resulted in a favourable response.

Conclusion: Immunocompromised patients often exhibit mucocutaneous involvement, which is uncommon in immunocompetent individuals without specificity, leading to diagnostic difficulties. Although the patient lived in a non-endemic region, a travel history to Gangetic Plains, an endemic area for histoplasmosis, was elicited. Therefore, a comprehensive patient history is essential for diagnosis, in addition to microbiological and histopathological results.

Keywords: Histoplasmosis, Disseminated Histoplasmosis, Mucocutaneous Histoplasmosis

1. Background

Histoplasmosis is a granulomatous fungal disease, caused by *Histoplasma capsulatum*, an intracellular dimorphic fungus found in mycelial form in soil (25 °C) and yeast form at body temperature (37 °C), usually found in soil contaminated with bird excreta and bat guano; source of infection being aerosolized microconidia inhalation.^{1,2}

Histoplasmosis is mainly seen in tropical and temperate climatic regions. In the Midwestern US, incidence is estimated at around 6.1 cases per 100,000 population, the highest worldwide.³ In India, histoplasmosis is endemic in West Bengal and Gangetic Plains with prevalence varying from 0-12.3%.⁴

The most common clinical presentation is acute or chronic Pulmonary Histoplasmosis, which may resemble community-acquired pneumonia, tuberculosis, or malignancy. In patients with compromised immune systems, histoplasmosis frequently manifests as a disseminated disease, which may arise as a complication of an initial pulmonary infection, either from exogenous reinfection or the reactivation of a dormant source. Conversely, in individuals with competent immune systems, around

95% of pulmonary infections remain asymptomatic. Certain patients can progress to disseminated disease in which cutaneous lesions are usually seen in 4-11% of immunocompromised patients.¹

2. Case Presentation

A 56-year-old male was admitted to the Dermatology department of ESI-PGIMS Basaidarapur, New Delhi in April 2023, with the complaint of erythematous rashes all over his body along with ulcerative lesions in the oral cavity for around 45 days. To begin with, slightly elevated pin-head-sized skin lesions appeared on the face, which gradually spread to the trunk, limbs, and palate. These lesions further increased in size and coalesced to form multiple large erythematous plaques associated with watery discharge and crusting (Figure 1A & 1B). There were no complaints of itching associated with rashes.

The patient also gave a history of a single episode of fever with generalized weakness and myalgia. He was a known case of Type II diabetes mellitus and hypertension on oral hypoglycaemic and antihypertensive medications respectively. The patient had pulmonary tuberculosis in

the past (Three years ago) for which he had received a complete antitubercular treatment course.

On examination, the patient was well-oriented with stable vitals. On dermatological examination, multiple erythematous indurated plaques of varying sizes with overlying atrophy were present all over the body with the largest plaque measuring approx. 3x3 cm and smallest approx. 0.5x0.5 cm respectively. Few plaques showed central crusting and necrosis. Relative sparing of the axilla and genital area was seen. Examination of oral mucosa also revealed erythematous plaque with crusting over the soft palate. Mild pallor and the presence of right deep cervical lymphadenopathy were also observed. Systemic examination was found to be unremarkable.

The patient was currently residing in Delhi, however, on a detailed enquiry, it was revealed that he had travelled to his hometown, Gorakhpur, Uttar Pradesh and during the visit, had come into contact with poultry; approximately two months before the onset of his current symptoms.

A varied array of differential diagnoses like Parapsoriasis, Sarcoidosis, Cutaneous Leishmaniasis, Non-Hodgkin B cell lymphoma, or Disseminated Tuberculosis was listed as per clinical presentation of the patient. He was symptomatically treated with antibiotics (Amoxicillin-clavulanic acid combination and ceftriaxone) for secondary infection of skin lesions.

Chest X-ray revealed opacity in the right upper zone,

haziness in the right lower zone, and patchy opacities in the left middle and lower zone. The PET CT- scan revealed consolidations in the right upper and lower lobe with paratracheal and bilateral hilar lymphadenopathy along with hepatomegaly.

Laboratory evaluation revealed the presence of anaemia (Hb-8.6 g/dl), normal WBC count with raised ESR, raised fasting blood sugar and HbA1c was 9.1. The LFT and KFT were within normal limits. The viral markers [HIV/hepatitis C/hepatitis B] were found to be non-reactive.

The sputum sample came negative for *Mycobacterium tuberculosis* by Ziehl Neelsen staining and by molecular method (Truenat for *M.tb*). The blood culture was sterile after incubation for five days (BacTAlert/Biomerieux).

Punch skin biopsy taken from the left flank on KOH-Calcifluor mount showed narrow base budding yeast cells and on histopathological examination (Figure 2A), the presence of granulomatous inflammation with lymphocyte cuffing in the dermis was observed. Both intracellular and extracellular capsulated yeast forms of fungus (2-5 µm) were seen and found to be Periodic Acid Schiff (PAS)-positive (Figure 2B & 2C). Based on the microscopic findings, Real-time PCR was performed on biopsy tissue using the gene target: mitochondrial small subunit RNA of *Histoplasma capsulatum*, which came out to be positive. Urine test for Histoplasma galactomannan antigen urine (by lateral flow assay) was also positive.



Figure 1. A) Facial plaques exhibiting central crusting & necrosis. B) Numerous plaques present on the entire back with crust formation. C & D) The patient's clinical images demonstrating positive response to therapy, indicating notable improvement.

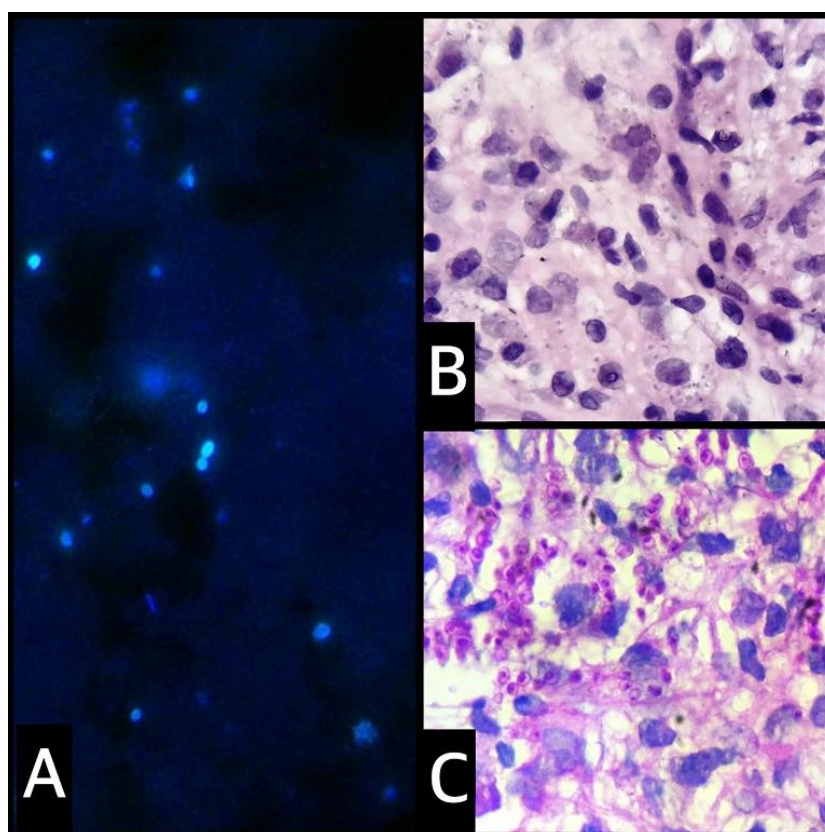


Figure 2. A) KOH- mount depicting narrow-based budding yeasts. B) Histopathology revealing intracellular & extracellular capsulated yeast forms of around 2-5 μ m size (H&E, x100). C) Periodic acid-Schiff stain (PAS) showing PAS-positive capsulated yeast forms.

Fungal culture of the skin biopsy specimen, after four weeks of incubation, showed white cottony colonies on Sabouraud Dextrose Agar (SDA) at 25 °C (mycelial form) and brownish, yeast-like colonies on Brain Heart Infusion blood Agar at 37 °C. Lacto-phenol cotton blue staining done on the mycelial colonies from SDA showed large, rounded, thick-walled, single-celled, tuberculate macroconidia formed on short, undifferentiated conidiophores.

After being finally diagnosed with disseminated cutaneous histoplasmosis with lung involvement, the patient was put on IV Liposomal Amphotericin B for three weeks followed by Itraconazole (oral) for six months. The patient responded well to the treatment and was found to considerably improve during the treatment follow-up (Figure 1C & 1D).

5. Discussion

We report a case of progressive disseminated histoplasmosis based on clinical suspicion combined with microbiological and histopathological findings with no apparent evidence of immune suppression. Perhaps, in this case, uncontrolled diabetes may have contributed to the development of disseminated disease, similar to the case reported by Kumari et al.⁵

In immunocompetent hosts, disseminated histoplasmosis usually occurs as pulmonary infection with oral ulcers, nodules, and vegetative plaques, which are seen in this case too. Reasons for widespread dissemination remain

unknown in 20-70% of cases.⁶

Cutaneous lesions exhibit diverse presentations that lack specificity, including mucocutaneous erosions/ulcers or multiple erythematous papules/nodules accompanied by scaling or crusting.⁷ In this case, there are several erythematous plaques of varying sizes, these manifestations resemble the lesions in disseminated tuberculosis, sarcoidosis, or cutaneous Leishmaniasis, thereby posing a diagnostic challenge. Hence, microbiological and histopathological findings are crucial in establishing a definitive diagnosis of the disease. Table 1 displays several instances of disseminated histoplasmosis with cutaneous involvement documented in previous decade in India, all successfully treated due to prompt diagnosis and specific therapy.

Although the studied patient was a resident of a non-endemic area, he was likely contracted to the infection while visiting his hometown situated in the Gangetic plains (endemic area for Histoplasmosis) and also has a history of contact with poultry; therefore, the history of residence/travel in endemic areas as well as contact to the probable source must be elicited.

Although the gold standard method for diagnosis is culture, its practical use is frequently restricted as it requires Biosafety Level-3 (BSL-3) and is time-consuming, delaying appropriate treatment and representing a potential health risk for laboratory workers. Histopathological observation of fungal structures in tissues requires skilled personnel, as several protozoa and fungi may be challenging

Table 1: Cases of Disseminated Histoplasmosis with Cutaneous Involvement Documented in Previous Decade in India

Case	Age/Sex	Presenting symptoms with duration	Underlying comorbidity	Diagnostic modality	Treatment & Outcome	Ref
1	9/M	Multiple small brownish to black colored, raised, painful lesions over face, upper & lower limb X 3 weeks	HIV+	Skin Biopsy	Amphotericin B f/b Itraconazole Cured	10
2	42/M	Multiple painful ulcerated lesions over the face, neck, tongue, arms, trunk, and genitalia X 8months	HIV+	Skin biopsy	Amphotericin B f/b Itraconazole Cured	11
3	65/F	Multiple painful red elevated lesions over the face and trunk with oral cavity erosions, fever, weight loss, cough X 5months	Rheumatoid arthritis on Methotrexate	Skin biopsy	Itraconazole Cured	7
4	65/F	Multiple papulo-nodular lesions with adherent crusting over abdomen, neck, back & thigh X 2months	-	Skin biopsy	Amphotericin B f/b Itraconazole Cured	12
5	37/M	Diffuse erythematous papules over right thigh & right supraclavicular region X 20 days	-	Skin biopsy	Amphotericin B Cured	13
6	46/M	Fever, weight loss, multiple reddish papules X 5months	-	Skin scrapping, bone marrow biopsy	Amphotericin B f/b itraconazole Cured	14
7	48/F	High-grade fever, generalized papulonodular lesions with ulceration & scaling X 2 months	Type 2 Diabetes mellitus	Skin biopsy, bone marrow aspiration	Amphotericin B f/b itraconazole Cured	5
8	46/M	Intermittent low-grade fever, weight loss, ulcerated lesions in oropharynx X 4months	-	FNAC submandibular lymph node	Itraconazole Cured	6
9	32/M	Single well defined punched out ulcer over the thigh X 3 months	-	Skin biopsy	Amphotericin B f/b itraconazole Cured	6
10	50/M	Erythematous plaques over forehead and tongue X 1 month	Pulmonary Tuberculosis	Skin biopsy	Amphotericin B f/b itraconazole Cured	15
11	22/F	Generalized erythematous papules with fever, joint pain & weight loss	-	Skin biopsy	Amphotericin B f/b itraconazole Cured	15
12	59/M	Generalized reddish skin lesions X 5 months	-	Skin biopsy	Ketoconazole Cured	16

to differentiate from *Histoplasma*. Molecular methods have shown their usefulness in rapid diagnosis; therefore, PCR can be used as a tool for early diagnosis to initiate early treatment. Specific antigen detection tests can serve as a valuable supplementary method for diagnosing histoplasmosis. Nevertheless, it is important to note that antigen tests may exhibit cross-reactions with other fungal infections, and their sensitivity is reduced in individuals with a competent immune system.⁸

6. Conclusion

The incidence of histoplasmosis in India is underappreciated and it has been suggested that it may not be rare but underdiagnosed.^[9] The clinical similarity of tuberculosis and histoplasmosis is probably one of the reasons for underdiagnosis in developing countries along with the limited facilities for fungal detection.

Author Contributions

SM: Study conceptualization; SM, BA, JA, RG: Methodology; BA: Writing Original draft; SM, RG, JA: Review & editing; BA, IX, VS: Test performance and validation; BA, JA, VS:

Data curation. All authors read and approved the final manuscript.

Conflict of Interest Disclosures

All authors declared that they have no conflict of interest.

Ethical Approval

Study has been approved by Institutional Ethical Committee of ESI-PGIMSR, Basaidarapur, New Delhi.

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