

# Primary oral histoplasmosis in an immunocompetent host masquerading as malignancy

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## Abstract

*Histoplasma capsulatum* is known to cause deep mycotic infections, the primary site being pulmonary, and may disseminate in immunosuppressed patients. Oral presentation is usually a part of disseminated disease however may rarely occur as an isolated event. Extensive literature search has shown that only 17 cases of primary oral histoplasmosis in immunocompetent hosts have been reported from India to date. We hereby report a rare case of primary oral histoplasmosis in a middle-aged, non-diabetic, and HIV-negative patient masquerading as malignancy.

**Keywords:** Histoplasma, immunocompetent host, oral mucosa

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## INTRODUCTION

Histoplasmosis, also known as Darling's disease, is a systemic mycotic infection caused by *Histoplasma capsulatum*.<sup>[1]</sup> Infections are endemic in central and northern parts of the United States, South America, Indonesia, and Malaysia; however, sporadic cases are found worldwide.<sup>[1,2]</sup> Primarily a pulmonary pathogen, histoplasmosis may disseminate to involve extrapulmonary organs in immunodeficient patients. Histoplasmosis in Indians tends to more commonly affect the extrapulmonary sites, particularly the oral cavity.<sup>[2]</sup>

Though oral histoplasmosis is usually associated with the chronic disseminated form of the disease, it rarely presents as a primary oral infection in HIV-negative patients without any underlying illness. Only 17 cases of primary oral histoplasmosis in immunocompetent hosts from India have been reported to date.<sup>[3]</sup> We hereby report another rare case of oral histoplasmosis in an otherwise healthy patient.

## CASE REPORT

A 43-year-old male presented to the ENT outpatient department with a complaint of painful mouth ulcer of 4 months duration, which gradually increased in size. On clinical examination, an irregularly shaped ulcero-proliferative growth involving the left buccal mucosa was noted. The lesion was grey-white, indurated, tender and did not bleed on touch [Figure 1a]. Physical examination did not show any local or systemic lymphadenopathy or any organomegaly. A biopsy was performed on the lesion and sent for histopathologic examination in view of suspected malignancy.

The biopsy was processed entirely. Hematoxylin and eosin-stained sections showed tissue lined by stratified squamous epithelium with focal ulceration. Subepithelial tissue showed sheets of histiocytes with granulomatous

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inflammation [Figure 2a]. On higher magnification, numerous 2-4  $\mu\text{m}$  sized, round to oval, narrow-based single budding yeast cells surrounded by a pale halo were seen both intracellularly within histiocytes and extracellularly, which was consistent with *H. capsulatum* [Figure 2b]. Special stains including periodic acid Schiff (PAS) and Gomori methenamine silver (GMS) highlighted similar forms [Figures 3a and 3b]. The stain for acid-fast bacilli was negative. Based on typical histomorphological features, a final diagnosis of oral histoplasmosis was made.

The patient was reassessed to look for any signs of dissemination. There was no history of cough, skin lesions or significant weight loss. Chest X-ray was normal. There was no history of travel to endemic regions. The patient was a non-diabetic and non-smoker. There was no history of intake of any immunosuppressant drugs. The serum sample of the patient was subjected to HIV serology as per Strategy III of the National AIDS Control Organisation, which returned negative. He was started on oral Itraconazole 200 mg OD for 12 weeks, following which the lesions resolved completely [Figure 1b]. The patient was kept on follow-up for the subsequent 3 months with no signs of recurrence.

## DISCUSSION

*Histoplasma* spp. is a dimorphic fungus which grows in the filamentous form at 28°C (saprophytic phase) and yeast form at 37°C (parasitic phase). It is a natural habitat of soil, found particularly at sites contaminated with bird or bat droppings. Species known to cause human infections include *H. capsulatum* var. *capsulatum* and *H. capsulatum* var. *duboisii*. A third variety, *H. capsulatum* var. *farciminosum* is an equine pathogen found in Africa.<sup>[1]</sup>

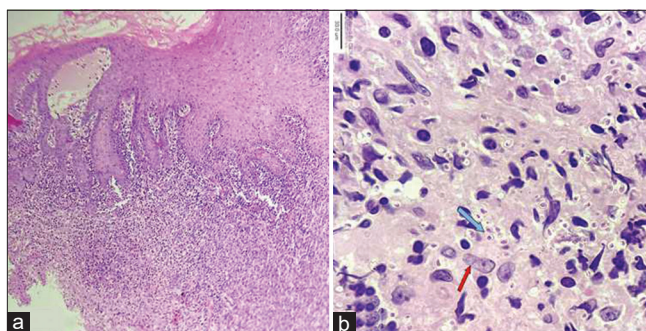
Infection is acquired by inhalation of conidia which germinate to produce yeast forms which then replicate within the reticuloendothelial system. Pulmonary infection can either be self-limiting or may further progress to chronic disease, particularly in patients having underlying lung pathology, with or without cavitations. Wu ES *et al.*,<sup>[4]</sup> in their study, showed a higher rate of infection in patients with pulmonary tuberculosis than in healthy people or patients with other pulmonary diseases. Any sex and age can be affected though most cases have been previously reported in males and in young adults.<sup>[3,5]</sup> Our patient was a middle-aged male working in a municipal corporation where he was frequently exposed to soil contaminated with excreta of poultry and pigs, explaining the possible source of infection. Dissemination to extrapulmonary sites may occur in patients with immunocompromised states

such as HIV, diabetes, alcoholism, extremes of age and post-radiotherapy for malignancy; however, no risk factor is identified in about 20% of the patients.<sup>[6]</sup> There were no signs of dissemination in our patient.

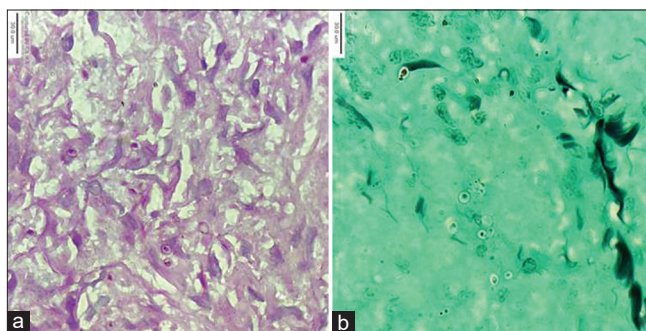
Oral manifestation of histoplasmosis as a part of the disseminated process could either be an early or sometimes the only presentation of disease. Direct inoculation of buccal mucosa by fungus could be a reason for primary oral infection.<sup>[3,7]</sup> The lesions of oral cavity may have a variable presentation, including indurated, vegetative, furunculoid papulo-nodular or plaque-like lesions, a



**Figure 1:** (a) Clinical image shows a grey white indurated lesion on left buccal mucosa (b) Clinical image shows near complete resolution of lesion 6 weeks post treatment



**Figure 2:** (a) Tissue lined by stratified squamous epithelium, subepithelium showing dense chronic inflammation with histiocytic preponderance, H&E, 100x (b) Microphotograph showing intracellular and extracellular yeast forms of *Histoplasma* surrounded by a clear halo (blue arrow) along with histiocytes (red arrow), H&E, 400x



**Figure 3:** (a) Yeast forms of *Histoplasma capsulatum* highlighted on PAS stain, 400x (b) Yeast forms of *H. capsulatum* highlighted on GMS stain, 400x

shallow or deep painful ulcer with a pseudomembrane being the most common.<sup>[2,3]</sup> Tongue, palate, gingiva, buccal mucosa and lips are amongst the most frequently affected sites.<sup>[1-3]</sup> These lesions may be misinterpreted as aphthous and/or traumatic ulcers, ulcerative gingivitis or stomatitis, tuberculosis, necrotising sialometaplasia, other deep mycoses or even malignancies such as squamous cell carcinoma and lymphoma.<sup>[3,7]</sup> Isolated oral presentation of histoplasmosis, as in our case, can clinically and pathologically mimic malignancy.<sup>[6]</sup>

Diagnosis can be made by histopathologic examination and culture, the latter being the gold standard. The histopathological presentation may vary from exuberant necrosis with mild chronic inflammation and dense collection of histiocytes to well-formed granulomas.<sup>[6]</sup> Differentials include bacterial infections such as tuberculosis and other fungi such as candida, cryptococcus, pneumocystis, toxoplasmosis and microforms of Blastomyces.<sup>[6]</sup> Special stains like PAS and GMS can be helpful in highlighting the fungal elements. Serology and histoplasmin test have a limited role, especially in HIV patients, where direct immunofluorescence is a more useful tool.<sup>[5]</sup> Itraconazole is the drug of choice with lesser side effects than amphotericin B.

Hence we conclude that pathologists must be aware of the histomorphological features of histoplasmosis and should always keep it as a differential diagnosis while examining

biopsies from oral ulcerative lesions, as misdiagnosis of malignancy may lead to unnecessary surgical interventions with potentially disastrous consequences. Early diagnosis and prompt treatment can be life-saving for the patient.

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#### Conflicts of interest

There are no conflicts of interest.

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