J Oral Res
research in oral sciences

REVIEW

CLINICAL AND HISTOPATHOLOGICAL PRESENTATION OF HISTOPLASMOSIS IN THE ORAL CAVITY - A SYSTEMATIC REVIEW

Presentación clínica e histopatológica de la histoplasmosis en la cavidad oral: una revisión sistemática

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ABSTRACT

Objective: Oral lesions can be an early indicator of systemic histoplasmosis, especially in immunocompromised patients. The main aim of this review was to summarise demographic and clinical findings and correlate them with histopathological findings.

Material and Methods: The literature search included articles published on oral histoplasmosis from databases like *PubMed*, *Scopus*, *Web of Science*, and *EMBASE*. The included articles provided information regarding sociodemographic and clinical data, human immunodeficiency virus (HIV) infection status, histopathological features, treatment, and outcome. This review included 30 case reports encompassing a total of 92 individual cases, of which 34 were HIV-positive.

Results: The oral manifestation was observed as a disseminated form in all HIV patients. Oral histoplasmosis is clinically presented as a painful ulcerated lesion commonly seen in the tongue, gingiva, palate, and buccal mucosa. Histopathologically, sheets of histiocytes with yeast-like cells, inflammatory infiltrate, and multinucleated giant cells were seen. Histopathological findings are essential for an early diagnosis of oral histoplasmosis since it could mimic other diseases clinically. Itraconazole was found to be an effective treatment for oral histoplasmosis.

Conclusions: Oral lesions of histoplasmosis can occur in non-endemic countries and immunocompetent individuals. Histopathological findings are essential for an early diagnosis of oral histoplasmosis since it could mimic other diseases clinically.

Keywords: *Histoplasmosis; Oral manifestation; Histoplasma capsulatum; Immunohistochemistry; HIV infections; Systematic review*

Received: January 04, 2024. | **Accepted:** August 24, 2025. | **Published online**: October 28, 2025.

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doi:10.17126/joralres.2025.016

RESUMEN

Objetivo: Las lesiones orales pueden ser un indicador temprano de histoplasmosis sistémica, especialmente en pacientes inmunodeprimidos. El objetivo principal de esta revisión fue resumir los hallazgos demográficos y clínicos y correlacionarlos con los hallazgos histopatológicos.

Material y métodos: La búsqueda bibliográfica incluyó artículos publicados sobre histoplasmosis oral en bases de datos como *PubMed, Scopus, Web of Science* y *EMBASE*. Los artículos incluidos proporcionaron información sobre datos sociodemográficos y clínicos, el estado de infección por el virus de la inmunodeficiencia humana (VIH), las características histopatológicas, el tratamiento y el pronóstico. Esta revisión incluyó 30 informes de casos que abarcaban un total de 92 casos individuales, de los cuales 34 eran VIH positivos.

Resultados: La manifestación oral se observó como una forma diseminada en todos los pacientes con VIH. La histoplasmosis oral se presenta clínicamente como una lesión ulcerada dolorosa que se observa comúnmente en la lengua, la encía, el paladar y la mucosa bucal. Histopatológicamente, se observaron láminas de histiocitos con células levaduriformes, infiltrado inflamatorio y células gigantes multinucleadas. Los hallazgos histopatológicos son esenciales para el diagnóstico precoz de la histoplasmosis oral, ya que podría simular clínicamente otras enfermedades. El itraconazol demostró ser un tratamiento eficaz para la histoplasmosis oral.

Conclusiones: Las lesiones orales de histoplasmosis pueden presentarse en países no endémicos y en personas inmunocompetentes. Los hallazgos histopatológicos son esenciales para el diagnóstico precoz de la histoplasmosis oral, ya que podría simular clínicamente otras enfermedades.

Palabras clave: *Histoplasmosis; Manifestaciones bucales; Histoplasma capsulatum; Inmunohistoquímica; Infecciones por VIH; Revisión sistemática*

INTRODUCTION

Histoplasmosis (Darling's disease) is a common systemic fungal disease caused by the thermally dimorphic fungus called Histoplasma capsulatum. Histoplasmosis is a self-limiting infection primarily affecting the lungs.[1] Extra-pulmonary involvement is seen often in immunosuppressed individuals.[2] The disseminated form is associated with HIV or immunosuppressed patients and affects multiple organ systems.[3] Males are affected more due to high exposure rates in occupations with soils. Average age involvement is higher in older adults. Histoplasmosis is common in endemic areas of America, Africa, India, and Southeast Asia.[4] Globally, it is more prevalent in tropical and subtropical regions but can be found worldwide.

Histoplasma capsulatum exists in two forms: a mycelial form in the environment and a yeast form at body temperature. Initially, it begins with inhaling the fungal spores from the contaminated, most acidic, and moist nitrogen-rich soils containing the excrement of livestock, bats, or birds. Once inhaled, the spores reach the alveoli, where they are phagocytosed by alveolar macrophages and convert to yeast form. The immune response plays a crucial role in controlling the infection.

However, if cellular immunity is compromised, such as in immunocompromised patients, infections can disseminate hematogenously, affecting various organs.[5] Symptoms can vary from acute to chronic pulmonary involvement with diffuse infiltration of the lung, causing respiratory failure, shock, and leading to multi-organ failure.

Oral histoplasmosis can be the first or earliest manifestation of systemic histoplasmosis infection. The oral involvement could present as the initial manifestation of the disease or as an associated chronic disseminated infection. It is characterized by multiple painful ulcers or granular ulcerated lesions, crater-like, non-healing, and erythematous, mostly on the buccal mucosa, palate, tongue, and gingiva. In 30% - 50% of cases, histoplasmosis manifests as a disseminated form.[6]

Oral histoplasmosis possesses diagnostic difficulties in oral medicine or oral and maxillofacial surgery departments when manifested in non-endemic countries and immunocompetent individuals since it clinically mimics other infections or malignancies.[7] Several cases were not noticed or misdiagnosed as tuberculosis, syphilis, or other malignant lesions, especially in countries like India.[2] Histoplasmosis can only be ruled out from other diseases by early biopsy and appropriate histopathological findings. The main aim of this review is to summarise demographic and clinical findings and correlate them with histopathological findings. Oral manifestations are usually the starting point for diagnosing and treating oral histoplasmosis.

MATERIALS AND METHODS

Protocol

A systematic literature search was performed independently, and standard PRISMA guidelines protocol for Systematic Reviews and Meta-analyses updated in 2020 were followed in this review.[8]

Research Question

The research question was designed based on the PICO format: "What are oral manifestations in patients with histoplasmosis?"

P (Population)

Patients with oral histoplasmosis.

I (Intervention)

Clinical and histopathological features of oral histoplasmosis.

C (Comparison)

Patient presenting with oral manifestation of histoplasmosis and other patients.

O (Outcome)

Clinical: Lesion type (ulcer/nodule), location (palate/tongue), symptoms (pain/bleeding).

Histopathological: Granuloma formation, Inclusion bodies, special stains.

Search Strategies

Electronic literature searches were carried out manually in databases *PubMed, Scopus, Web of Science, EMBASE, Google Scholar* databases, and grey literature to identify studies that matched the following MESH Terms ("Histoplasmosis" OR "Histoplasma fungal infection" OR "Histoplasmoses" OR "Histoplasma capsulatum" OR "Infection Histoplasma" OR "Histoplasma capsulatum Infection" OR "Infection Histoplasma Capsulatum" OR "Histoplasma capsulatum Fungal Infection") AND ("oral cavity" OR "oral" OR "mouth" OR "vestibule" OR "cavitas oris" OR "mouth cavity proper" OR "oral cavity proper" OR "oral manifestations") for identifying articles published between January 2001 and December 2024.

Eligibility Criteria

The inclusion criteria for the selection of the article were:

Human studies.

Articles published only in English.

Clinically and histopathologically diagnosed cases of oral histoplasmosis.

Articles published between January 2001 and December 2024.

Case reports & series (n=28), cross-sectional (n=1) and retrospective study (n=1) were

included. The exclusion criteria for this study were: Narrator review or systematic reviews, meta-analyses, *in-vitro* studies, animal studies.

Articles not in the English language.

Articles not in the English language, articles with only abstracts or without full text, studies with insufficient clinical and histopathological data of oral histoplasmosis, cases with histoplasmosis in other regions, and cases with histoplasmosis accompanied by other infections or tumors were excluded, (Figure 1).

Literature Screening

A two-step procedure was performed in this literature screening. First, all the recognized titles and abstracts were extracted and preliminarily screened for inclusion in the full-text review. Second, the inclusion and exclusion criteria indicated above were used to determine if entire texts were eligible.

The screening was independently carried out by two authors (PK and TD). Any discrepancy was resolved by the third author (DB). The PRISMA flowchart depicts an overview of the literature search and screening processes (Figure 1).

Summary measures

This review focuses mainly on demographic data like mean age, sex predilection, exposure history, associated systemic complications, a common site of location, characteristics, signs and symptoms of oral lesions, time of evolution, and histopathological features of oral histoplasmosis

Data Extraction and Management

The sociodemographic and clinical data of the patient, history, human immunodeficiency virus (HIV) infection status, other systemic complications, histopathological features, other investigations, treatment, and outcome were extracted from all the included articles.

Statistical analysis

The data collected was analyzed using Statistical Package for the Social Sciences (SPSS).

RESULTS

Literature selection

We identified 1546 articles in total, including 579 from *PubMed*, 354 from *Scopus*, 287 from *Web of Science*, and 326 from *EMBASE*. 865 articles were selected after screening the duplicate records, and from this, 486 were excluded by reviewing titles and Abstracts, 379 articles were selected, out of which 354 were excluded for reasons like papers not in English (n=116), non-relevant to the topic (n=67), narrative review or comment article (n=23), Abstract only (n=51), book chapters or recommendations (n=38), and articles with insufficient clinical or histopathological data (n=59) were excluded. In this review, 30 articles with a total of 92 cases were included.

Sociodemographic Information

Of 30 articles, seven (23.33%) were from the United States, India, and Brazil, two (6.66%) were from the UK, France, and Australia, and one (3.33%) was from China, Italy, and Sri Lanka. The mean age was 51.05±13.52, in these, 75 (81.5 %) were men, and 17 (18.47 %) were women, with significantly higher male predilection than females with 2:1, Male: Female ratio given in Table 1.

Systemic complications

Oral histoplasmosis is a significant clinical marker for systemic complication and an indicator of disseminated histoplasmosis. Among

92 cases, 60 (65.21%) cases reported systemic complications. Most commonly, 16 (17.29%) had a history of pulmonary involvement such as acute tuberculosis,[9,10] chronic tuberculosis, pneumonia, and *Pneumocystis jirovecii*.

Thirty-four cases (34.78%) had HIV infection,[11,18] three (3.26%) had hepatitis, two (2.17%) had diabetes, lupus erythematosus and one (1.08%) had other complications like mycosis, multiple sclerosis, rheumatoid arthritis and cholecystectomy. A total of 32 cases (34.74%) had no systemic complications (Table 2), and seven cases (7.60%) were associated with bilateral lym-phadenopathy involving submandibular, cer-vical, submental, and jugular carotid regions.

Clinical features

Clinically, it appeared as a painful, erythematous ulcerated lesion with a granular surface and irregular margins covered by a non-specific grey membrane. The most commonly involved site was the tongue (32.6%) and the hard palate (23.91%), followed by the soft palate (13.08%), the gingiva (7.6%), the alveolar mucosa (8.69%), the buccal mucosa and lip (6.52%) and the pharynx (1.08%).

Figure 1. The PRISMA flowchart depicts an overview of the literature search and screening processes.

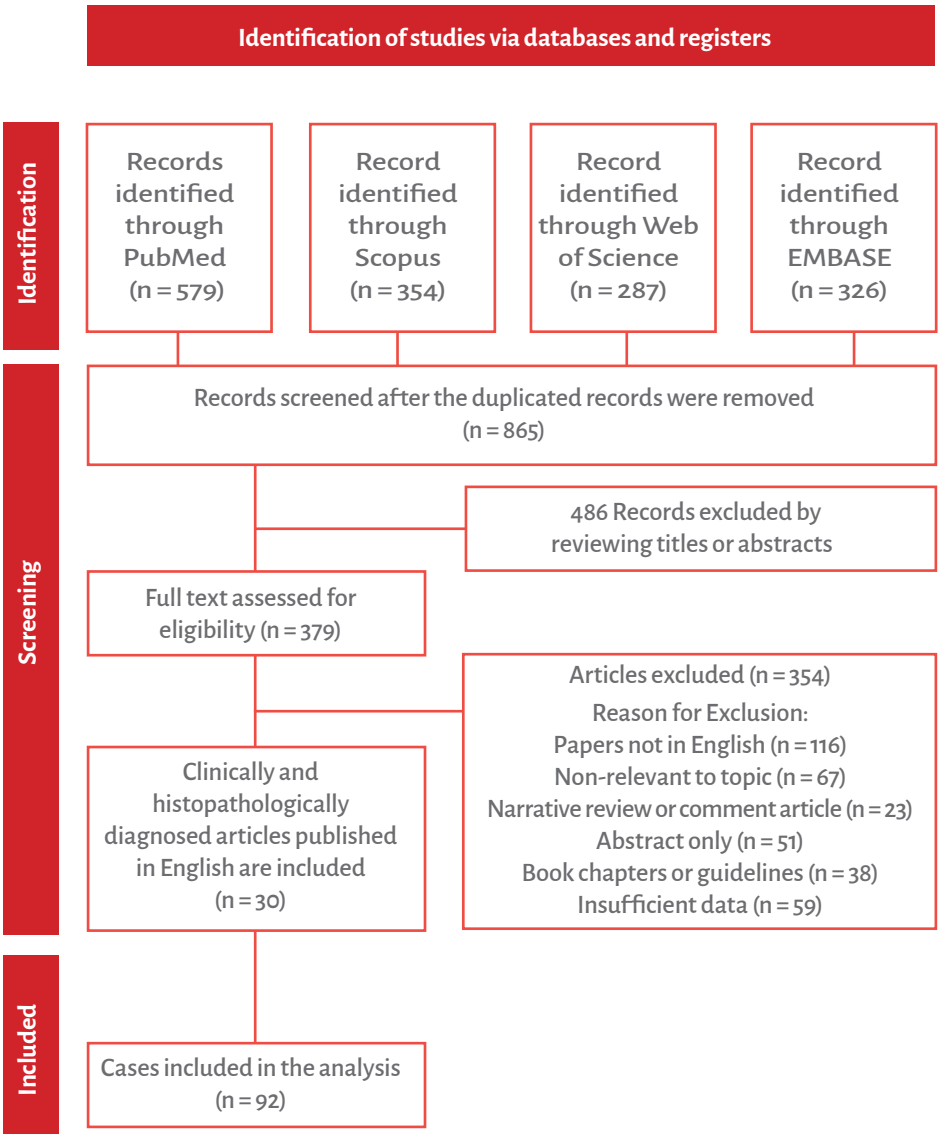

Table 1.

Summary of case reports related to oral histoplasmosis.

Author, Year Country	Type of study	Patient Details	History	Clinical Findings	Other Systemic Findings	Histopathologic Findings	Other Investigations	Treatment	Outcome
Mignogna[40] 2001 Italy	Case report	44 year, Male	Anorexia, Weight loss, pulmonary disease	Size: 4 × 2.5 cm in diameter. Site: posterior lateral border of the tongue, Signs: Ulcerated with rolled margins and an irregular surface.	---	---	PAS & Gms -1–2 µm yeasts found.	Fluconazole 200 mg	Cured, 90 days of follow up
Smith[7] 2006 Australia	Case report	58 year, Male	Pneumoconiosis (previously greater than 200 g per day, currently 40 g / day).	Site: lower gum, a submucosal lesion in the left cheek.	Pulmonary, chronic liver disease.	Epithelium - hyperplasia CT-Inflammatory cells, Granulomatous, Multinucleated giant cells.	PAS - Round to ovoid pale nucleifound.	Itraconazole 200 mg twice daily	Cured, no follow up
Narayana[27] 2009 United States	Case report	75 year, Female	Type 2 diabetes mellitus, Cho lecystectomy, Hypertension, Rheumatoid arthritis.	Site: ulceration of gingiva and mucosa. Size: extending. from teeth 22 to 27. Signs: facial and lingual tissues were indurated, and interspersed with white areas.	Submental lymph nodes	CT - Inflammatory cells, few multinucleated giant cells.	GMS – not mentioned	Itraconazole intravenously for 4 days	Cured, patient is doing well 4 months following diagnosis
Patil[22] 2009 India	Case report	45 year, Male	---	Site: left tongue, Size:1.0 × 2.5 cm. Sign: solitary, large, deep ulcer and floor appears granular covered with slough with focal areas of necrosis.	---	Epithelium-Ulcerated, CT-Chronic inflammatory cells, epithelioid cell granulomas, few Langhans-typegiant cells, and foamy macrophages.	---	Itraconazole 200 mg	Cured, 12 weeks of followed
Ge[20] 2010 China	Case report	51 year, Male	---	Size: 3 cm Site: Right & left soft palate, extendingto the hard palate. Signs: crater-like ulcers inflamed base.	---	CT–Chronic inflammatory cells, granulomatous lesion with epithelioid macrophages.	SDA - septate hyaline hyphae, PAS – yeast cells	Oral itraconazole 200 mg twice daily.	Cured, 6 months follow up

Table 1 continues on the next page →

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Author, Year Country	Type of study	Patient Details	History	Clinical Findings	Other Systemic Findings	Histopathologic Findings	Other Investigations	Treatment	Outcome
Fortuna[21] 2011 USA	Case report	67 year, Male	---	Size: Large erythematous lesion Site: hard palate. Signs: elevated, ulcerated, micropapillary surface, and irregular margins	---	CT - Inflammatory cells - plasma cells & lymphocytes. Small granulomas with Langhans-type giant cells.	---	Itraconazole 200 mg orally	Not mentioned, 2 months follow up
de Paulo[18] 2012 Brazil	Case series	35 year, Male	---	Site: lateral border of the tongue. Signs: Ulcerated lesion with a granular surface.	---	CT -Focally ulcerated mucosa containing a few multinucleated giant cells. Numerous small circular yeast-like bodies.	GMS - Small circular yeast-like bodies	Not mentioned	Not mentioned, No follow up
		70 year, Male	---	Site: tongue. Signs: Large erythematous lesion with an elevated, ulcerated, reddish surface, and irregular margins.	---				
		50 year, Male	---	Site: Tongue Signs: Two crater-like ulcers with inflamed base and elevated hard borders.	---				
Mohammed[12] 2012 India	Case report	35 year, Male	HIV is a chronic smoker and and has had a history of alcohol intake for twenty years.	Site: Right lateral tongue. Size: 2 cm in diameter. Sign: Ulcer was non-tender, indurated, with rolled-up margins.	Cervical lymphade-nopathy. inflammatory and oval, 2 – 4 µm intracellular, budding yeast-like cells.	Inflammatory cells - Chronic	LPCB -culture showing numerous hyphae, white mycelial growth.	Oral fluconazole 800 mg	Cured, 20 months of follow up
Vidyanath[35] 2013 India	Case report	73 year, Male	---	Site: labial mucosa, lateral borders of tongue, hard & soft palate. Signs: Painful ulcerated and necrotic lesions covered by a pseudomembrane.	Bilateral submandibular lymphadenopathy.	CT-Epithelioid cell granulomas with numerous histiocytes, multinucleated giant cells. Small round to oval cell with halo.	GMS – Not Mentioned	Liposomal amphotericin B , oral itraconazole 200 mg	Cured and 1 year follow up
Brazão-Silva[19] 2013 Brazil	Case report	43 year, Male	---	Site: gingival papillae between lower central incisors Sign: ulcerative areas covered by a pseudomembrane.	Diffuse nodular, irregular opacities in both lungs.	CT – Langhans-type multinucleated giant cells, Inflammatory cells-lymphocytes and and neutrophils.	GMS - single budding form. LPCB-hyphae, tuberculate.	Itraconazole 200 mg.	Cured 5 months follow-up.

Table 1 continues on the next page →

Author, Year Country	Type of study	Patient Details	History	Clinical Findings	Other Systemic Findings	Histopathologic Findings	Other Investigations	Treatment	Outcome
Mehta[14] 2013 USA	Case report	28 year, Male	---	Site: buccal mucosa. Size: 6×10 cm Sign: irregular, indurated, ulcer with yellowish discharge, slough at the ulcer base.	Left submandibular lymphadenopathy, HIV, hepatosplenomegaly.	CT - Epithelioid granulomas resembling sign et rings, due to the double wall of the organism.	GMS - outlines the double wall of Histoplasma.	Itraconazole , antiretroviral therapy.	3 months, cured.
Iqbal[29] 2014 Australia	Case report	58 year, Male	---	Site: buccal mucosa, gingival. Sign: painful, non-healing ulcer.	---	CT – Chronic inflammatory, numerous intracellular microorganisms surrounded by a clear halo.	PAS, GMS - presence of small intracellular yeast-like cell	Amphotericin Itraconazole	Cured, 12 weeks follow-up.
Folk[28] 2017 USA	Case report	44 year Female	Systemic lupus erythematosus	Size: Irregularly shaped ulcer Site: gingiva of the anterior mandible.	Primary -pulmonary infection, Secondary tuberculosis	CT – Inflammatory Cells, peripheral pale zone (halo).	GMS/PAS-Not mentioned	Not Mentioned	Cured, No follow-up
Souza[23] 2017 Brazil	Case report	81 year, Male	Smoking, chronic obstructive Pulmonary disease (SCOPD), Asthma, Arthrosis.	Size: 25-mm. Sign- granular ulceration with red -yellow areas. Site: Hard & Soft palate.	Early -pulmonary involvement, Later- acute respiratory failure.	CT – diffuse infiltrate of epithelioid macrophages / Inflammatory cells.	GMS - small particles of H. capsulatum	Itraconazole 200 mg/day	Patient did not survive
Kamboj[43] 2017 USA	Case report	81 year, Female	HIV disease chronic hepatitis B.	Site: tongue, hard palate. Sign: painful ulcer.	---	Multiple intracellular yeast forms.	GMS -intracellular yeast-like cell.	Amphotericin B , itraconazole.	Cured, 7 months follow-up
Chrobocze[10] 2018 France	Case report	52 year, Male	HIV, pulmonary tuberculosis, pneumocystis, chronic obstructive pulmonary disease (COPD).	Site: Base of the tongue and the soft palate pillars Sign: Necrotic ulceration.	Pulmonary military, bronchial dilatation of right lung.	CT-Inflammatory cells, granulomatous, lymphocytes.	PAS, GMS– yeasts like cells.	Itraconazole 400 mg, antiretroviral	Cured, 6 month follow-up
Khetarpal[34] 2019 India	Case report	39 year, Male	---	Site: buccal, Palatal mucosa, gingiva. Signs: Ulcer indurated, grey pseudomembrane, necrosis, bone loss.	Bilateral submandibular lymphadenopathy.	CT- epithelioid cell granuloma, multinucleated giant cells. Small round, oval cells surrounded by a clear halo.	GMS, PAS-Numerous circular yeast-like cells	Amoxicillin, Metronidazole, Oral itraconazole.	Cured, 1 year follow-up
Medina[17] 2024 Brazil	Case report	39 year, Female	---	Site: Hard and soft palates. Sign: ulcerated lesions with irregular borders	pulmonary and hepatic involvement. HIV with immunosuppression, hematological abnormality	Ulcerated epithelium. CT- chronic inflammatory cells infiltrate, numerous plasma cells, histiocytes, lymphocytes	GMS - large number of small oval yeast-like structures	Amphotericin B, deoxycholate, fluconazole	Cured, 6 years follow -up

Table 1 continues on the next page →

Author, Year Country	Type of study	Patient Details	History	Clinical Findings	Other Systemic Findings	Histopatho-logic Findings	Other Investigations	Treatment	Outcome
Sharma[11] 2012 London lling.	Case report	51 year, Male	Cough, hemoptysis	Site: lower left edentulous ridge Signs: Ulcer, swe-	Submandibu-lar lymphade-nopathy.	CT – Chronic inf-lammatory cells.	---	Prednisolone, oral itracon-azole	Cured, 6 weeks follow-up
Klein[30] 2016 Brazil	Case report	32 year Female	Mycosis	Site: Tongue Signs: painful ulcer	Oral candi-diasis	CT - chronic in-flammatory in-filtrate, perinu-clear halo.	GMS – yeasts like fungi.	Not mentioned	5 months follow-up, cured
Sigera[9] 2019 Sri Lanka	Case report	56 year, Male	Diabetes me-llitus, Chronic obstructive pulmonary disease	Size: 2 × 4 ×1 cm. Site: left poster-ior tongue. Sing: solitary, tender, irregular ulcer re-move with indu-ration.	bacterial pneumonia	Inflammatory cells-macrop-hages, neutro phils, and pla-small cells.	PAS, GMS-small oval yeast-like cells.	Itraconazole, Intravenous amphotericin B.	The patient The did not survive, 1-month follow-up.
Qureini[42] 2019 USA	Case report	36 year, Female	Weight loss	Site: Gingiva. Sign: Necrotizing ulcerative gin-givitis.	---	Small hyper-chromatic or-ganisms surr-ounded by a clear halo.	GMS, PAS-mo-re organisms noted	Amphotericin B ,Itracona-zole	Not mentio-ned
Stefan[13] 2022 USA	Case report	62 year, Male	HIV , Pneu-mocystis jirovecii	Site: Hard and soft palates. Sign: irre-gular-appearing mass	---	CT-Budding ye-ast forms con-sistent with H. capsulatum	---	Amphotericin B ,Itracona-zole.	Not mentio-ned.
Dogenski[36] 2022 Brazil	Case report	39 year, Male	Lupus ery-the matosus	Site: Tongue Sign: ulcerated lesion	---	CT-Multinucle-ated giant cells. Chronic infla-mmatory cell.	---	Betametha-sone cortico-steroid, Ke-toconazole	Cured, 2 years follow -up
Guttal[25] 2023 India	Case report	40 year, Male	---	Site: Tongue Size: 1 x 1 cm SIGN: Solitary de-ep irregular-sha-ped ulcer.	---	Epithelium -hy-perplastic with ulceration CT -yeast-like bodies with a clear halo.	PAS - Dense acute and ch-nic inflamma-tory cell	Fluconazole, antiretroviral therapy.	Not mentio-ned.
Singh[6] 2023 India	Case report	43 year, Male	---	Site: left buccal mucosa Sign: Irregularly shaped, ulcero-proliferative gro-wth	---	Epithelium: fo-cal ulceration. CT: Granuloma-tous inflamma-tion, yeast cells with clear halo	PAS, GMS: High -lights yeast forms of cap-sulatum	Itraconazole	Cured, 3-month follow-up.
Kumar[31] 2023 India	Case report	65 year, Male	Bilateral sub-mandibular lymphadeno-pathy	Site: tongue Size: 5 x 4 cm Sign: irregularly shaped ulcer, oe-dematous and raised	---	CT: Inclusion bo-dies with a pe-ripheral halo, multinucleated giant cells, ly-mphocytes, and plasma cells. cells within	PAS, GMS: int-racytoplasmic circular yeast-like cells	Itraconazole	Cured, 12 weeks follow-up.

Table 1

Author, Year Country	Type of study	Patient Details	History	Clinical Findings	Other Systemic Findings	Histopathologic Findings	Other Investigations	Treatment	Outcome
Sanjeevi[33] 2024 USA	Case report	65 year, Female	Multiple sclerosis with fingolimod treatment	Site: Tongue Sign: Ulcerated lesion.	CD4 lymphocytopenia due to fingolimod.	Epithelium: hyperkeratosis CT: Inflammatory cell infiltrate, multinucleated giant cells, epithelioid macrophages, perinuclear halo.	PAS, GMS: clusters of budding yeast cells within a macrop hage.	Itraconazole	Cured, 12 month follow-up
Noratikah[15] 2018 Malaysia	Retrospective study (1995-2016)	n= 39 Mean age, 57.8 Male 35 Female 4	n= 12 HIV: 7 TB: 4 Hepatitis: 1	Sign: Ulcer (n= 22) Swelling (n=13). Site: Tongue=13 Gingiva =7, Palate =8, Alveolar=8, Buccal mucosa=7, Lip=2, Floor of mouth, fauces= 1, Buccal sulcus= 3.	Immunosuppression=14, Focal= 23, Multiple= 12.	Inflammation - 25, Granulomatous infection - 14.	GMS , PAS-39	Amphotericin B, Itraconazole	---
Couppié[16] 2002 France	Crosse-ctional study (1991-1998).	n=21 Mean age = 37.8 Male 15 Female 6	HIV – 21	Sign: Erosive, hemorrhagic crust Site: Palate 4, Tongue 1, Lip 4 Pharynx 1,	Pulmonary 16, Multiple 7, Single 4	---	---	Amphotericin -B 7, Itraconazole 13, Fluconazole 1	1-6 months follow-up

HIV: Human immunodeficiency virus. **PAS:** Periodic acid Schiff. **LPCB:** Lactophenol cotton blue. **CT:** connective tissue. **GMS–Grocott:** Gomori's methenamine silver stain. **n:** number of patient. **TB:** Tuberculosis.

Table 2.
General characteristics of included oral histoplasmosis cases.

Characteristics		n (%)	
Age (mean ± S.D)		51.05 ± 13.52	
Sex	Male	75 (81.53)	
	Female	17 (18.47)	
Type of Study	Case-report study	27 (90)	
	Case series study	1 (3.33)	
	Cross-sectional study	1 (3.33)	
	Retrospective study	1 (3.33)	
Prevalence	India	7 (23.33)	
	Brazil	7 (23.33)	
	USA	7 (23.33)	
	France	2 (6.66)	
	Australia	2 (6.66)	
	UK	2 (6.66)	
	China	1 (3.33)	
	Italy	1 (3.33)	
	Malaysia	1 (3.33)	
	Sri Lanka	1 (3.33)	
Systemic Complications	Pulmonary	16 (17.39)	60 (65.21)
	HIV	34 (34.78)	
	Hepatitis	3 (3.26)	
	Diabetes	2 (2.17)	
	Lupus erythematosus	2 (2.17)	
	Mycosis	1 (1.08)	
	Rheumatoid arthritis	1 (1.08)	
	Multiple sclerosis	1 (1.08)	
	No systemic complications	32 (34.79)	

Table 3.
Common site, histopathological, special stains, treatment, and outcome of oral histoplasmosis cases.

Characteristics		n (%)	
Site	Tongue	30 (32.6)	
	Hard palate	22 (23.91)	
	Soft palate	13 (13.08)	
	Gingiva	7 (7.60)	
	Buccal Mucosa	6 (6.52)	
	Alveolar mucosa	8 (8.69%)	
	Lip	6 (6.52)	
	Pharynx	1 (1.08)	
Single site involvement		31 (33.69)	
Multiple site involvement		28 (30.45)	
Not mentioned		33 (35.86)	
Histopathological	Histiocyte-like clear halo	10 (10.86)	
	Yeast like cells	19 (20.65)	
	Epithelioid granuloma	24 (26.08)	
	Giant cells	11 (14.13)	
	Langhans giant cell	3 (3.26)	
Special stains	Grocott–Gomori's methenamine silver stain	10 (10.86)	**66 (71.73)**
	Periodic acid Schiff	4 (4.34)	
	Grocott–Gomori's methenamine silver stain & Periodic acid Schiff	49 (53.26)	
	Lactophenol cotton blue	2 (2.17)	
	Sabouraud 's Dextrose Agar*	1 (1.08)	
	Not mentioned	26 (28.29)	
Treatment	Itraconazole	54 (58.69)	**89 (96.73)**
	Fluconazole	5 (5.43)	
	Amphotericin B	24 (26.08)	
	Amphotericin B + Itraconazole	5 (5.43)	
	Ketoconazole	1 (1.08)	
	Not mentioned	3 (3.24)	
Outcome	Cured	26 (28.26)	
	Not mentioned	64 (69.56)	
	Did not survive	2 (2.17)	

*: Not a stain.

Table 4.
Clinical differential diagnosis for a chronic non-healing ulcer.

Ulcer type	Clinical features
Traumatic ulcer	Painful ulcer, covered by a grey necrotic membrane and surrounded by an inflammatory halo with firm, elevated borders.
Tuberculosis ulcer	Irregular, superficial, or deep, painful ulcer with granular base, undermined edge.
Syphilitic ulcer	Painless, smooth, ulcerated nodule covered by a greyish-white membrane and indurated margins
Malignant ulcer	Nodular, punched-out ulcer with irregular shapes, uneven or rolled borders, raised edge, indurated base, and fixed lymphadenopathy

Table 5.
Histopathological Differential Diagnosis of Oral Histoplasmosis.

Differential diagnosis	Histopathologic features
1. Blastomycosis	Connective tissue - Giant cells, macrophages, and typical round organisms. Organisms - Budding, have a doubly refractile capsule, micro-abscess.
2. Coccidioidomycosis	Connective tissue -Large mononuclear cells, inflammatory infiltration, and foci of coagulation necrosis are often found in the center of the small granulomas, with multinucleated giant cells scattered throughout the lesion. Organisms - Found in the cytoplasm of the giant cells, endospores within the large spherules are identified.
3. *Cryptococcus neoformans*	Connective tissue - Multinucleated giant cells . Small organisms with a large clear halo, described as 'tissue microcyst,' found singly or in groups scattered throughout the granuloma.
4. Tuberculosis	Connective tissue - Formation of granuloma exhibiting foci of caseous necrosis surrounded by epithelioid cells, lymphocytes, and occasional multinucleated giant cells.
5. Sarcoidosis	Connective tissue - Nests of epithelioid cells, with multinucleated giant cells. Granuloma ultimately transforms into a solid, amorphous, eosinophilic, and hyaline mass as it ages. Chief microscopic features: fibrous granulomatous nodules. (contain T and B cells, Ig).
6. Systemic lupus erythematosus	Epithelium - Hyperkeratosis with keratotic plugging, atrophy of the rete pegs, liquefaction, degeneration of the basal layer of the cell. Connective tissue - Perivascular infiltration of lymphocytes and dermal appendages and basophilic degeneration of collagen and elastic fibers, with hyalinization, edema, and fibrinoid change.

Over one third of cases (34.78% or 34/92) were HIV-positive, they clinically had painful ulcers with an indurated border and multiple nodular lesions, as well as fever, malaise, and weight loss. Disseminated histoplasmosis was seen in all HIV patients. 19 (20.65%) patients had immunosuppression either due to immunosuppressant medication, diabetes mellitus, or immunosuppression related to alcoholism.

Histopathological features

All the cases, histopathologically, had typical features like pseudo-epitheliomatous hyperplasia of the mucosal epithelium in association with connective tissue containing mixed inflammatory infiltrate consisting of macrophages, neutrophils, and plasma cells.[19]

A fifth of cases (20.65%) had budding yeast-like cells with intracytoplasmic inclusion bodies called histiocytes, and 10.86% had small round, oval cells with peripheral clear cell halo. Over a quarter (26.08%) had epithelioid granulomas, and 14.13% had multinucleated giant cells; of these, three cases show Langerhans-type giant cells.

Other Investigation

In this review, several studies were examined to confirm the presence of the organism; in 10.86% of the cases, Grocott-Gomori methenamine silver (GMS) was done, in 4.34% Periodic acid-Schiff (PAS) staining was done, and in 52.17 % of cases both GMS and PAS were done for confirmation of organism.

In 2.17 % of 2 cases, Lactophenol cotton blue culture (LPCB) was done,[13,20] and in 1.08 % of cases, Sabouraud 's Dextrose Agar (SDA) was done.[21] In 28.29 % of cases, no other special investigations were done[12,14,17,22,23] given in Table 3.

Outcome

Of all 92 cases, there was a substantial or total resolution of the oral symptoms in 44.56%; in two cases, the patient did not survive,[10,24] and in 47.82 % of cases, the outcome was not mentioned.

The follow-up period was from one month to two years (51.8 %), and in four cases (14.8%), follow-up was not mentioned. In HIV-positive patients, in 33 cases, there was a significant remission, and in one case, the outcome was not mentioned.

DISCUSSION

Histoplasmosis commonly affects immunocompromised patients and is endemic throughout the Mississippi and Ohio valleys in south and central USA, Western Africa, and Southeast Asia. Globally, it is more prevalent in tropical and subtropical regions but can be found worldwide.[25] In our review, oral histoplasmosis was reported commonly in India, Brazil, and the USA.

Exposure to *Histoplasma capsulatum* spores is a major cause of histoplasmosis. The fungus is prevalent in damp soil with high organic content and with bird and bat droppings. Males are more susceptible because of higher exposure rates to this soil work such as construction, remodeling, demolition, farming, exposure to contaminated soil, poultry coops, and cave excavation, which can result in the inhalation of fungal spores and people with a history of travel to endemic regions.[26] Similarly, our review showed a higher prevalence in males than in females, with a mean age of 51 years.

After inhalation of spores, mycelial form converts into yeast form, phagocytosed by alveolar macrophages and replicates intra-

cellularly. Dectin-1 is a macrophage receptor that recognizes β-glucan in the *Histoplasma* cell wall. It produces β-linked glucans to surround and conceal α-glucans to avoid this host reaction. (Hsp60), a heat shock protein present on the yeast cell walls permits the entry of yeast into macrophages with the CR3 receptor found on host macrophages without provoking inflammation. As the host immunity response develops, yeast growth ceases within 1-2 weeks after exposure.

With further maturation of the cell-mediated response, delayed-type hypersensitivity response to *Histoplasma* antigens occurs, typically 3-6 weeks after exposure. The inflammatory response produces granulomas with areas of necrosis over weeks to months. In immunosuppressed individuals, fungus multiplies within macrophages, and hematogenous spreads to other organs.[27] In certain cases, macrophages enclose the fungus, and at a later stage, it is reactivated.[28]

Histoplasmosis can manifest in acute, chronic, and disseminated forms. Acute histoplasmosis is a diffuse pulmonary infection that is self-limiting and more common than chronic histoplasmosis. The chronic type clinically resembles tuberculosis, upper-lobe infiltration rates and cavitation are seen in chest roentgenograms.[29]

However, in our review, chronic histoplasmosis was found to be more common than the acute form. Disseminated histoplasmosis is easily distinguished by its spread to extrapulmonary regions.[30]

Extra-pulmonary regions like the spleen, lymph nodes, adrenal glands, gastrointestinal tract (GIT), liver, central nervous system (CNS), and kidneys are mostly affected. Both chronic and disseminated forms mainly affect immunosuppressed patients, including transplantation, chronic renal disease, prolonged use of corticosteroids, and acquired immune deficiency syndrome (AIDS). In HIV-infected patients, the prevalence of cutaneous and oral lesions is more common.[31] In our review, patients had immunosuppression either due to HIV infection, intake of immunosuppressive drugs, Type 2 diabetes mellitus, or immuno-suppression due to alcohol use or were aged over 54 years.[32] Recently, the use of fingolimod has caused CD4 lymphocytopenia due to lymphocyte redistribution and, as a result, could predispose patients to immuno-suppression and opportunistic infections.[33] The occurrence of disseminated histoplasmosis in HIV seropositive patients is less common as compared to that occurrence in endemic areas.[34]

Clinically, oral histoplasmosis occurs as a painful ulcerated lesion that is non-healing and crater-like with a granular surface and irregular margins. It mostly occurs in the buccal mucosa, gingiva, tongue, and palate. Focal or multiple sites are affected.[6] The compiled data in our study also demonstrates ulcers as the most common clinical presentation occurring in the dorsal surface of the tongue and hard and soft palate. In HIV patients, it occurs as a painful ulcerated area and is sometimes covered by a grey membrane that is indurated with elevated and rolled-up margins, similar to a malignant ulcer.[35]

Histoplasmosis in an immunocompetent patient, with discrete oral presentation, that initially mimicked acute necrotizing ulcerative gingivitis. Gin-gival biopsy will confirm the diagnosis of histoplasmosis.[36] Histopathological diagnosis is the primary investigative modality that provides clear confirmation of the infection.[37] A typical characteristic feature is a pseudo-epitheliomatous hyperplasia of the mucosal epithelium.

The connective tissue shows diffuse lymphocytic infiltration and other inflammatory cells, such as plasma cells and neutrophils. Sheets of histiocytes (macrophages) disrupt the normal tissue structure, and areas of cell death (necrosis) are evident. Within the cytoplasm of these histiocytes are numerous small (2-4 µm) yeast-like cells, strongly suggestive of H. capsulate organisms. Epithelioid granuloma and multinucleated giant cells can be prominent. All patients in our review had diffuse lymph histiocytic infiltration.

Histoplasma capsulatum can be visualized using various staining techniques. Routine stains like Hematoxylin and eosin (H&E) are used. Special stains like Periodic acid-Schiff (PAS) and Gomori methenamine silver (GMS) highlight the cell walls of fungi with crescent-shaped nuclei.[38] Potassium hydroxide (KOH) is a strong alkali, is used as a primary screening tool, and dissolves the tissues surrounding the fungi so that the hyphae of fungi can be seen clearly under a microscope. This wet-mount procedure helps to visualize fungal elements but does not necessarily identify the species of fungi.[39] Calcofluor white, a fluorescent stain, binds to chitin in the cell walls and aids in identifying organisms. Giemsa and Wright's stains can detect *H. capsulatum* yeast cells in blood smears.

Slide culture of Lactophenol cotton blue mounts of Histoplasma colonies produces a high number of hyaline hyphae and a low number of tuberculate macroconidia. In Sabouraud's Dextrose Agar, white mycelial growth can be observed. For subacute and chronic types of histoplasmoses (including mediastinal histoplasmosis), the most common method used for diagnosis is antibody testing, where circulating antibodies are present and sensitive for the detection of antigens in serology tests.[40] Compared to conventional diagnostics, molecular methods provide higher analytical specificity and are less time-consuming.[41] However, no FDA-approved molecular tests for *H. capsulatum* are presently available for clinical specimens.

Several molecular targets have been used in laboratory-developed PCR assays. In the fluorescence *in situ* hybridization technique, *H. capsulatum* rRNA blood culture colonies were observed, and it gave a quick and definitive diagnosis.[42] Clinically, a histoplasmosis ulcer resembles other chronic non-healing ulcers like traumatic ulcer, tuberculosis, syphilitic, and malignant ulcer.
Histopathological differential diagnoses are blastomycosis, coccidioidomycosis, cryptococcus, tuberculosis, sarcoidosis, and systemic lupus erythematosus. A detailed differential diagnosis of oral ulcer is given in Table 4 and Table 5.

Histopathological findings are essential for an early diagnosis of oral histoplasmosis since it could mimic other diseases clinically. The traditional treatment remedy is itraconazole for mild to moderate histoplasmosis. Amphotericin B is the preferred drug for immunocompromised people suffering from severe pulmonary, disseminated, or limited illnesses.[43] Voriconazole and posaconazole are two new medications that are also effective. Spontaneous remission of oral histoplasmosis can occur with ketoconazole and itraconazole.

Even with effective therapy, there is still a chance of failure and recurrence, which will require long-term treatment for this disease.[44] However, if left untreated, this infection can lead to mortality in AIDS patients. For HIV-positive patients, anti-retroviral and anti-fungal therapy should be initiated. Acute histoplasmosis is a self-limiting condition that

does not require specific treatment except for symptomatic therapy with analgesics and antipyretics.[45] Itraconazole is used as a primary prophylaxis to reduce the incidence of histoplasmosis in people with CD4 counts <150 cells/mm^3.[46]

Patients should be clinically evaluated every 3 months for 1 to 2 years, even after the termination of therapy. Even if they are symptom-free, research indicates that they have a minimum chance of a 10%–20% chance of relapsing. The prognosis is variable depending on the systemic health status and severity of the infection. In our review, oral histoplasmosis was found to be fatal in two patients who had a disseminated infection.

CONCLUSION

Oral lesions of histoplasmosis can occur in non-endemic countries and immunocompetent individuals. Histopathological findings are essential for an early diagnosis of oral histoplasmosis since it could mimic other diseases clinically. To evaluate their prognosis in immunocompromised and immunocompetent individuals, more studies with a longer follow-up period are essential.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

ETHICS APPROVAL

Does not apply

FUNDING

This research was developed using the researchers' own resources and did not receive institutional funding.

AUTHORS' CONTRIBUTIONS

Poonguzhalnalli Kumar: Concept, design, definition of intellectual content, literature search, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review.

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ACKNOWLEDGEMENTS

None.

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PUBLISHER'S NOTE

All statements expressed in this article are those of the authors alone and do not necessarily represent those of the publisher, editors, and reviewers.

PEER REVIEW

This manuscript was evaluated by the editors of the journal and reviewed by at least two peers in a double-blind process.

PLAGIARISM SOFTWARE

This manuscript was analyzed Compilatio plagiarism detector software. Analysis report of document ID. 7e7599031c8b080fe80921d03d9d2fc6832d4487

ISSN Print 0719-2460 - ISSN Online 0719-2479
https://joralres.com/index.php/JOralRes

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