



## Oral Manifestations Associated to Paracoccidioidomycosis and Histoplasmosis

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### Abstract

**Objective:** To determine the frequency and clinical forms of oral manifestations associated to Paracoccidioidomycosis (PCM) and Histoplasmosis. **Material and Methods:** 481 medical records of outpatients referred to the Medical Mycology Department were reviewed since 2009 to 2016. Data were analyzed using descriptive statistical methods. **Results:** 47 (9.77%) cases had oral manifestations, 29 (61.70%) were associated to PCM and 18 (38.29%) to histoplasmosis. For PCM, male-female ratio was 8:1 and 1:1 for histoplasmosis. The average age for PCM was 48 years old and 53 for histoplasmosis. All the PCM patients had more than 1 oral structure affected: 44.82% were gingival lesions and 27.58% palate. In patients with histoplasmosis, 6 (33.33%) were lesions affecting palate and 6 (33.33%) involving tongue. For both entities, painful ulcers and granulomatous-like lesions were the most prevalent clinical forms; however, we observed a wide range of other oral manifestations. Regarding PCM patient's comorbidities, 3 (10.34%) cases had HIV/AIDS, 8 (27.58%) histoplasmosis and 2 (6.89%) carcinomas. Whereas the comorbidities of patients with histoplasmosis, 2 (11.11%) had HIV/AIDS and 1 (5.55%) had carcinoma. **Conclusion:** In endemic countries for both mycoses, dentists must be aware of patients with mouth lesions, take advantage of epidemiologic clues that suggest risk factors and be acquainted with all the current diagnostic tests in order to make a quick diagnosis and treatment in highly suspicious cases.

**Keywords:** Paracoccidioidomycosis; Histoplasmosis; Oral Manifestations.

## Introduction

Paracoccidioidomycosis (PCM) and Histoplasmosis are granulomatous, systemic, chronic and endemic mycoses in Venezuela; *Paracoccidioides brasiliensis* complex has only been reported in Latin America, whereas *Histoplasma capsulatum* is found in temperate areas around the world. They both show oral manifestations when hematic or lymphatic dissemination occurs [1-4].

These mycoses begin when the mycelial forms are inhaled; once in the lungs, they can be disseminated causing manifestations in lymph nodes, liver, bones, nervous system and mouth, among other structures. The host's immunological condition, habits and epidemiological background are valuable keys to establish the diagnosis [1,4-6].

Oral manifestations are polymorphic and can affect several structures, such as lips, gingival tissue, mouth floor, palate and tongue, causing the patient to visit the dentist or the physician. Furthermore, paracoccidioidomycosis and histoplasmosis are considered HIV/AIDS defining-illnesses in Latin America. Therefore, it is important to establish a casuistry and account of these diseases as differential diagnoses in endemic areas such as Venezuela [5-7].

The aim of this study was to determine the frequency and clinical forms of oral manifestations associated to both mycoses.

## Material and Methods

### Study Design

A retrospective and descriptive study was performed during the period of January 2009 to December 2016, based on data derived from outpatient cases of the Medical Mycology Department "Dr. Dante Borelli" in the Tropical Medicine Institute at Universidad Central de Venezuela, Caracas, Venezuela.

### Population

This study analyzed 481 patients with paracoccidioidomycosis and histoplasmosis, diagnosed by direct microscopic examination with Potassium hydroxide and Parker ink/Giemsa stain, isolation and culture of *Paracoccidioides brasiliensis* complex or *Histoplasma capsulatum*, biopsies (H & E/Gomori-Grocott) and/or serology test (agar gel immunodiffusion).

Inclusion criterion was: presence of any oral manifestations associated to these mycoses. Patients who had any or both of the diseases but did not have any oral structure affected were excluded. A database was made with demographic information, risk factors, chest X-ray findings and oral manifestations.

### Statistical Analysis

Data were analyzed using descriptive statistical methods.

## Results

Out of 481 clinical records found, 354 (73.59%) had diagnosis of histoplasmosis and 127 (26.40%) of paracoccidioidomycosis. Out of them, 70 (14.55%) had HIV/AIDS, out of which 63 (90%) related to histoplasmosis and 7 (10%) to PCM. 47/481 (9.77%) had oral manifestations from which 29/47 (61.70%) were associated to PCM and 18/47 (38.29%) to histoplasmosis.

Regarding PCM, 26 (89.65%) were male and 3 (10.34%) female, in an 8:1 proportion. The significant group was between 41 to 62 years old.

Reviewed records indicated that patients had more than one associated risk factor, such as smoking in 12 (41.37%) cases and previous contact with barnyard fowl or bats in 10 (34.48%), in 19 (65.51%) cases the data was not registered. As for occupation, 13 (48.82%) cases were farmers. On the other hand, histoplasmosis was the most reported comorbidity with 8 (27.58%) cases, followed by HIV/AIDS with 3 (10.34%) cases, in 19 (65.51%) patients the data was not registered (Table 1). Regarding the chest X-ray findings, interstitial pneumonitis was the most commonly reported pulmonary affection (Table 1).

**Table 1. Demography and epidemiological findings of patients with oral manifestations of PCM and Histoplasmosis.**

Variables	Paracoccidioidomycosis		Histoplasmosis	
	n	%	n	%
<b>Gender</b>				
Male	26	89.65	8	44.44
Female	3	10.34	10	55.55
Total	29	100.0	18	100.0
<b>Age Range</b>				
9 – 20	1	3.44	0	0.0
21 – 40	4	13.79	4	22.22
41 – 51	13	44.82	4	22.22
52 – 62	9	31.03	5	27.77
More than 63	2	6.89	5	27.77
Total	29	100.0	18	100.0
<b>Occupation</b>				
Farmers	13	44.82	5	27.77
Mechanics	3	10.34	0	0.0
Ground transportation	3	10.34	0	0.0
Mining	2	6.89	0	0.0
Construction	1	3.44	1	5.55
Housekeeping	1	3.44	0	0.0
Speleologist	0	0.0	1	5.55
Teacher	0	0.0	2	11.11
Hairstylist	0	0.0	1	5.55
Not register	6	20.68	8	44.44
Total	29	100.0	18	100.0
<b>Risk Factors*</b>				
Smoke	12	41.37	6	33.33
Contact with barnyard fowl or bats	10	34.48	7	38.88
Alcoholism	9	31.03	1	5.55
HIV/AIDS	3	10.34	2	11.11
Treatment with immunomodulators	0	0.0	2	11.11
Not register	19	65.51	3	16.66

**Comorbidity\*\***

HIV/AIDS	3	10.34	2	11.11
Carcinomas	2	10.34	1	5.55
Histoplasmosis	8	27.58	0	0.0
Parasitic diseases	2	6.89	0	0.0
Chronic Pulmonary Obstructive Disease (CPOD)	1	3.44	1	5.55
Osteoporosis	0	0.0	1	5.55
Lupus erythematosus	0	0.0	1	5.55
Psoriasis	0	0.0	1	5.55
Not register	19	65.51	11	61.13

**Chest X-Ray Findings**

Interstitial pneumonitis	23	79.31	14	77.77
Pulmonary fibrosis	1	3.44	0	0.0
Not register	5	17.24	4	22.22
Total	29	100.0	18	100.0

\*Some patients had more than one risk factor associated; \*\*Some patients had more than one comorbidity associated.

In relation to oral manifestations, the cohort exhibited more than one mouth structure simultaneously affected: 44.82% showed gingival lesions, 27.58% palate and 24.13% inner-cheek. As to clinical forms observed, the patients had more than one: 65.51% were deep painful ulcers and 65.51% granulomatous/moriform deep painful lesions (Table 2, Figure 1a, 1b and 1c).

**Table 2. Oral manifestations in patients with PCM and histoplasmosis.**

Variables	Paracoccidioidomycosis		Histoplasmosis	
	n	%	n	%
<b>Oral Structure Affected*</b>				
Gingiva	13	44.82	1	5.55
Palate	8	27.58	6	33.33
Inner cheeks	7	24.13	0	0.0
Lips	6	20.68	2	11.11
Alveolar ridge	5	17.24	4	22.22
Mouth floor	4	13.79	0	0.0
Tongue	2	6.89	6	33.33
Parotid	1	3.44	1	5.55
Maxillary tuberosity	1	3.44	0	0.0
Sub-mandibular region	0	0.0	1	5.55
Retro molar trigone	0	0.0	1	5.55
Tonsillar pillar	0	0.0	2	11.11
<b>Type of Lesion*</b>				
Deep painful ulcer	19	65.51	11	61.11
Granulomatous/moriform painful lesion	19	65.51	6	33.33
Painless tumor-like lesion	8	27.58	3	16.66
Macrochelia	4	13.79	1	5.55
Periodontitis-like lesion	4	13.79	1	5.55
Osteomyelitis	2	6.89	1	5.55
Parotitis	1	3.44	1	5.55
Non-painful red lesion	0	0.0	2	11.11
Bone exposure with necrosis	0	0.0	1	5.55

\*More than one type of lesion and oral structure affected.

In all cases of paracoccidioidomycosis (100%), mycological diagnosis was made by direct microscopic examination with Potassium hydroxide and Parker ink/Giemsa stain or biopsy (H & E/Gomori-Grocott/PAS stain). Culture was positive in 16 (55.17%) and serology in 19 (65.51%)

(Figures 2e, 2f, 2g and 2h). It was also observed 2 (10.34%) patients with PCM and carcinomas concurrently in the same oral lesion.

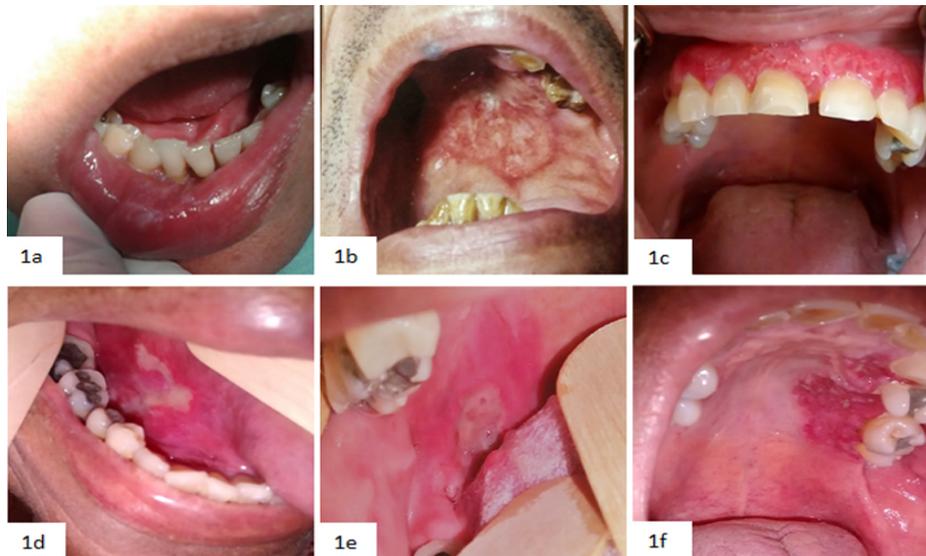


Figure 1. Oral manifestations associated to PCM (1a, 1b, 1c) and histoplasmosis (1d, 1e, 1f).

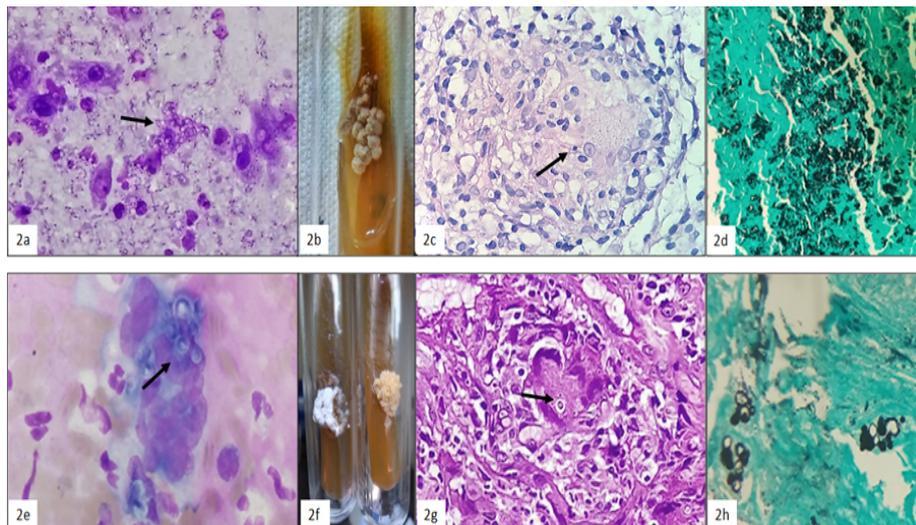


Figure 2. Microscopic findings in the diagnosis sequence for oral PCM and histoplasmosis respectively: Direct exam of the samples from oral lesions (2a, 2e), culture and isolation of the fungus from oral samples (2b, 2f), biopsy from oral lesions: H & E stain 400 X (2c, 2g), Grocott stain (2d, 2h).

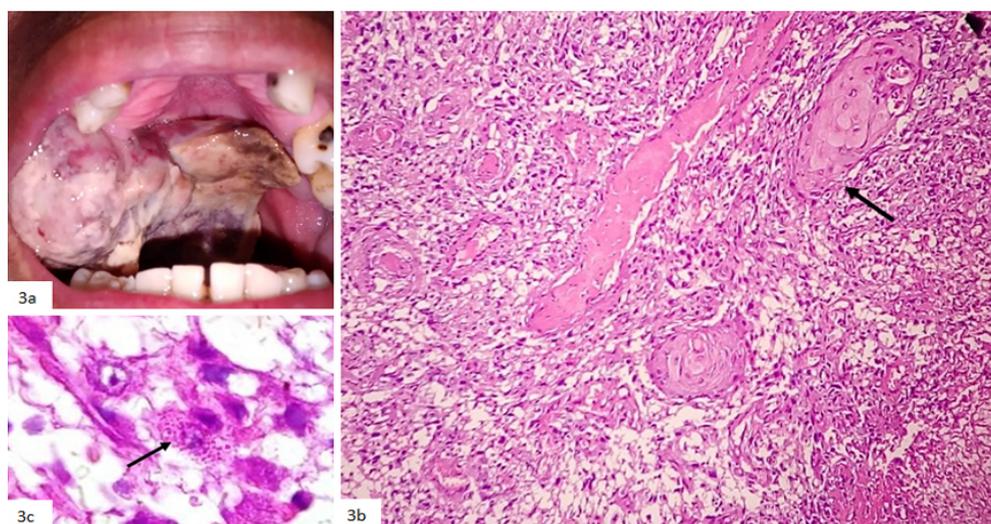
Regarding histoplasmosis, 8 (44.44%) were males and 10 (55.55%) females, in a 1:1 proportion. As for age range, the significant group was over 52 years old. The most important risk factors were previous contact with barnyard fowl or bats, in 7 (38.88%) cases, followed by smoking habit in 6 (33.33%) cases and HIV/AIDS in 2 (11.11%) cases. Similarly to PCM, most patients had bilateral pulmonary interstitial pneumonitis in their Chest X-rays (Table 1).

As for oral manifestations, more than one mouth structure was affected: 33.33% in palate, 33.33% in tongue and 22.22% in alveolar ridge. Similarly, more than one clinical form of oral

histoplasmosis was described, such as 61.11% deep painful ulcers, 33.33% granulomatous/moriform deep painful lesions and 16.66% tumor-like (Table 2) (Figure 1d, 1e, 1f).

In all cases of histoplasmosis (100%), mycological diagnosis was made by Giemsa stain or biopsy (H & E/Gomori-Grocott/PAS stain); culture was positive in 6 (33.33%) cases and serology in 9 (50%) (Figure 2a, 2b, 2c, 2d).

We reported 1 case of oral histoplasmosis associated to a neoplasia (poorly - differentiated squamous cell carcinoma with sarcomatoid areas). Clinically, it was observed a tumor lesion in the upper right alveolar tuberosity which emerged from a firm pedicle from the maxillary sinus; the biopsy reported malignant squamous cells with abrupt keratinization and spindles cells with cytologic atypia, necrosis areas and inflammatory infiltrate constituted by neutrophils, plasma cells, lymphocytes and foamy histiocytes with intracellular yeast forms of *Histoplasma capsulatum* (1000X) (Figure 3).



**Figure 3. Histoplasmosis and squamous cell carcinoma concurrently found in the same oral lesion. Clinical findings of the lesion (3a), H & E stain: Squamous cell keratinizing carcinoma (3b) and Intracellular yeast forms of *Histoplasma capsulatum* (3c).**

## Discussion

Paracoccidioidomycosis and Histoplasmosis are the most relevant endemic mycosis in Venezuela and both diseases frequently produce oral manifestations. Thus, dentists need to be aware of the clinical oral manifestations it causes in patients and take advantage of epidemiological clues that suggest risk factors for contracting these mycoses. Furthermore, dentists must be familiar with the use and limitations of the current diagnostic tests available for fungal diseases [1,7,8].

This study analyzed the epidemiological, clinical manifestations and diagnosis data of 29 (61.7%) patients with PCM and 18 (38.29%) with histoplasmosis, which had oral lesions.

According to gender and age we observed that PCM oral manifestations were more frequent in male patients, with 89.65% cases and age range of 41 to 62 years (75.85%), as it has been observed in earlier studies [5-7]. PCM oral manifestations occur at almost all ages, with highest incidence in

ages between 30 and 50 years in its chronic form (adult type), which is the most common in 90% of the cases, with classic signs and symptoms that include pulmonary and mucosal involvement [5,6]. In relation to gender, it has been reported that women have a stronger and greater immune response than men, which makes them more resistant to these mycoses. This immune response is probably associated to the levels of feminine hormone 17- $\beta$ -estradiol, as previously described [9].

In respect to histoplasmosis, we observed a uniform gender distribution with a 1:1 proportion, and an age range over 52 years old in contrast to previous authors, who found a male prevalence of 72.2% with a median age of 33.5 years; in addition, but they all had HIV/AIDS [8]. Histoplasmosis oral manifestations are less frequent and occur in the progressive disseminated form of the disease, mainly in HIV/AIDS or elderly patients (immunosenescence) [8,10].

Among risk factors related to the acquisition of PCM and histoplasmosis in this study, smoking habit is a frequent contributing factor and is present in 41.37% cases of PCM and 33.33% of histoplasmosis and this finding coincides with previous reports. In PCM, alcoholic habit was important in 31.03% of the cases, as previously described in Brazil [2,7]; whilst in cases of histoplasmosis only 5.5% of them were associated to such factor, similar to the findings described in Venezuela [1,11]. Other important risk factors for histoplasmosis are those related to fungal exposure by previous contact with bird or bat droppings: 38.88% of the cases involved such risk factor. Similar data was described in Brazil [2,7] and Mexico [12] for PCM and in Venezuela for histoplasmosis [1,11].

HIV/AIDS was another significant risk factor. Histoplasmosis has long been recognized as an important opportunistic infection in patients with HIV/AIDS living in endemic regions all over the world [13-17]. In Venezuela, it is the most common mycosis among those with CD4 counts below 200 cell/mm<sup>3</sup> [1,8,11,16,18].

Also, it is known that HIV/AIDS patients frequently develop disseminated histoplasmosis and therefore oral lesions. The incidence of HIV/AIDS and histoplasmosis, according to the literature is between 1.4% and 85% [1,16,18]. In our country, as well as throughout the world, the frequency of mucosal manifestations in AIDS patients is not known, due to the fact that only sporadic cases have been reported. On the other hand, in cases of PCM, the association with AIDS is strongly increasing. In this study it was found 10.34% of prevalence; in contrast, some researchers do not report any case of HIV/AIDS coinfection [6]. Therefore, the dentist should always suspect immunosuppression in patients with PCM or histoplasmosis oral manifestations, due to the fact that these mycoses can be AIDS/HIV-defining illnesses [1,5,10,11,17,19].

Another important risk factor for both mycoses, particularly, histoplasmosis, is treatment with immunomodulators, such as TNF- $\alpha$  [14,15]. In this study, 2 patients had been treated with these drugs. It is important to consider that several patients had more than two risk factors.

According to other coinfections, we found 27.58% cases with PCM and histoplasmosis simultaneously. Conversely, a previous study reported that this association is rare [20]. A possible explanation could be attributed to the outbreak of ecologic and weather changes, possibly leading to

the hypothesis that both fungi inhabit in the same ecological niche. In fact, in Venezuela, PCM reservareas and endemic areas of histoplasmosis are geographically underhanded.

In this study, it was also found that 2 patients had PCM and squamous cell carcinoma (SCC) in the same lesion. To this respect, other authors referred 84.5% of this association, frequently reported in the respiratory and digestive tract [21-24]. Interestingly, we found 1 case with diagnosis of carcinoma in the same oral lesion of histoplasmosis. To the best of our knowledge, there are no previous reports of histoplasmosis and SCC concurrently in the same oral lesion.

Statistical analysis of oral manifestations in PCM, also showed more than one oral structure simultaneously affected, being the gingiva the more prevalent in 44.82% of the cases, followed by palate with 27.58%, similar to other reports in the literature [5,6]. Special mention must be made to 1 case of parotid involvement, which is not frequently described [25].

Regarding the type of oral manifestation, we observed more than one in each record, where deep painful ulcers and painful granulomatous-like lesions were the most frequent forms with 65.51% each one. Similar observations were reported in a study performed in Argentina, which included 21 PCM patients with oral manifestations [6].

Initially, these lesions appear as punctate hemorrhagic painful erosions; the progressive forms often involve extensive and erosive lesions that lead to osseous destruction whenever the gingiva is affected. Gingival retraction may cause exposure of the dental roots simulating periodontal disease. Ulcerations reveal a finely granular aspect including areas of proliferation, which can affect a large area of the oral cavity, including soft and hard tissue (bone), lips (macrochelia) and extra-oral structures by infiltration and tumefaction of the subjacent connective tissue. Chronic ulcers are usually painful and do not heal spontaneously; these ulcers characteristically have a red granulomatous or berry-like surface. In our cohort, 13.79% patients had macrochelia, which some authors report as a frequently observed manifestation in adult chronic multifocal PCM [5,6,24-27].

With respect to the cases of oral manifestations associated to histoplasmosis, the more affected structures were palate and tongue with 33.33% respectively, followed by alveolar ridge (22.22%); Some authors reported that commonly involved sites are tongue, palate, gingiva and lips [18]. However, other authors had similar results as us [13,28,29]. There are few and non-convincing reports of single oral histoplasmosis as a unique form of the disease; in those studies, there is not a conclusive explanation for the inoculation of the fungus directly in the oral cavity, and there are difficulties in determining the primary lung infection, which happens in many cases [18,28,29].

Concerning the type of oral manifestations, for histoplasmosis, it was observed a wide range of clinical forms in each record: 69.23% were painful ulcers, 38.46% were painful granulomatous-like lesions and 23.07% were tumor-like or indurated. These clinical characteristics concur with the reported by other authors [11,18,28,30]. It is appropriate to refer that in 2 cases, oral manifestations were not described as typical lesions: we found non-painful red macule lesions with presumptive diagnosis of subprosthetic stomatitis. Our 2 patients had important epidemiologic backgrounds,

which together with the dentist's high suspicion were decisive facts that allowed the diagnosis of histoplasmosis. As in PCM, we also reported macrochelia in histoplasmosis. Mucocutaneous lesions of both mycoses can be observed in any oral structure and may be polymorphic [13,17,29,30]. For this reason, they can be misdiagnosed as tuberculosis, SCC, leishmaniasis, among others. It is important for the clinician to communicate suspicion of a deep fungal disease to the pathologist, so that special staining and other diagnostic testing may be carried out [13].

## Conclusion

In Venezuela, as well as in other countries where PCM and histoplasmosis are endemic mycoses, dentists must have high suspicion in patients with oral lesions and always search for epidemiologic clues in order to include a strict evaluation of general health conditions during examination. This is sometimes neglected by a significant number of dentists, who are important professionals in the diagnosis of both mycoses, given that patients will frequently seek assistance for oral lesions and not respiratory symptoms, which are erroneously associated with smoking. A proper mycological examination of the lesions is a key tool to achieve the diagnosis and avoid torpid evolution of these diseases. Additionally, dentists must have the ability to suspect and diagnose HIV/AIDS and other immunosuppressive diseases in patients with oral manifestations of PCM and histoplasmosis.

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