

Oral manifestations of systemic fungal infections: 25-year experience in an endemic region

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ABSTRACT. Some mycoses are endemic. They develop through hematogenous spread, causing a generalized infection, usually with secondary mucosal involvement. The aim of this observational and retrospective study was to report the prevalence and characteristics of oral lesions in patients diagnosed with systemic fungal infections (SFI) over a 25-year period in southern Brazil. Demographic (age, sex, ethnicity, occupation) and clinical (anatomical location, symptoms, histopathological diagnosis and management) data from the medical records of patients with SFI were collected from 1995 to 2019. 34 cases of SFI were found, of which 31 (91.18%) were diagnosed as paracoccidioidomycosis (PCM) and 3 (8.82%) as histoplasmosis. Men were much more affected ($n = 31$; 91.18%), with an average age of 46.9 years. Most patients ($n = 18$; 58.06%) were Caucasian; 48% ($n = 15$) were farm/rural workers and the most affected region was the jugal mucosa ($n = 13$; 25.49%) followed by the alveolar ridge ($n = 12$; 23.52%). All patients with histoplasmosis were immunocompetent men (mean age: 52.67 years), and the palate was the most affected. All patients underwent incisional biopsy and were referred to an infectologist. The dentist has an essential role in the recognition of SFI, whose oral manifestations may be the first sign. SFI should be included in differential diagnosis in patients from endemic areas. In addition, the inevitable human mobility and globalization make knowledge of these mycoses necessary worldwide, especially since advanced cases in immunocompromised patients can be fatal.

Keywords: oral manifestations; mycoses; retrospective studies; paracoccidioidomycosis; histoplasmosis.

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Introduction

In systemic fungal infections (SFI), the gateway is a deep organ or site, such as the lung, gastrointestinal tract or paranasal sinuses (Carrasco-Zuber et al., 2016). The mycosis develops through hematogenous spread, causing a generalized infection, usually with secondary mucosal involvement. The most common global mycoses are caused by *Candida* spp. (superficial/cutaneous fungal infections), *Cryptococcus neoformans* and *Aspergillus* spp. (Sabol & Gumbo, 2008). Some dimorphic fungi are also associated, such as *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides* spp, and *Paracoccidioides brasiliensis*, (Colombo, Tobón, Restrepo, Queiroz-Telles, & Nucci, 2011; Berto, Wirth, Barth, & Hermes, 2018) as well as the subphylum *Mucoromycotina*, which causes Mucormycosis (Neville, Damm, Allen, & Chi, 2016).

Some of these mycoses are endemic. Humid geographical areas, with high rainfall and acidic soil conditions favor infection (Bicalho, Espírito Santo, Ferreira de Aguiar, & Santos, 2001). Paracoccidioidomycosis (PCM), for example, is a rare disease in the world, but is endemic to Latin America, with the highest prevalence in South America (Trindade et al., 2017; Tracogna et al., 2019). Histoplasmosis is most common in North America (Folk & Nelson, 2017). However, globalization and considerable human mobility in recent years highlight the importance of knowledge of these diseases worldwide, since they can have an aggressive course, especially in immunocompromised patients. Early recognition and management of histoplasmosis, e.g., are of paramount importance in maintaining health and prolonging life of HIV + patients (Economopoulou, Laskaris, & Kittas, 1998). As oral manifestations are usually the first signs of the disease, knowledge about its epidemiology, clinical and demographic characteristics is essential to avoid misdiagnosis and delays in treatment.

Considering the role of epidemiological studies in the prevention and treatment of diseases, the aim of this study was to report the prevalence and characteristics of oral lesions in patients diagnosed with SFI in an oral diagnostic referral service in southern Brazil over a 25-year period.

Material and methods

After ethical approval (CAAE 15561219.1.0000.0104), this observational and retrospective survey was conducted in accordance with the Declaration of Helsinki guidelines and according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) initiative (Elm et al., 2008).

Data from medical records of patients referred to the Service of Oral Diagnosis of the State University of Maringá (LEBU/UEM), state of Paraná, Brazil, from 1995 to 2019 were collected. Demographic (age, sex, ethnicity, occupation) and clinical (anatomical location, symptoms, histopathological diagnosis and management) of patients with SFI were recorded. Only patients with complete medical records and microscopically confirmed SFI diagnosis were included.

A database with variables was entered into Microsoft Excel 2010 (Microsoft Corp., Redmond, Washington, USA) for tabulation and statistical analysis. Data were evaluated using frequency and distribution tables, using IBM SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, New York, USA).

Results

General data

Of the 3,679 records, 38 (1.033%) presented some SFI. Four medical records were not properly filled out and were excluded. Therefore, 34 (0.924%) individuals were included. Men were much more affected ($n = 31$; 91.18%), and ages ranged from 28 to 69 years (average 46.9 years). Most of the individuals were Caucasian ($n=18$; 52.94%) and farm/rural workers ($n = 16$; 47.05%). 31 (91.18%) individuals were diagnosed with PCM and 3 (8.82%) with histoplasmosis. Although several cases of candidiasis were observed, all were superficial infections and were excluded from the analysis. The jugal mucosa and alveolar ridge were the most affected sites.

All patients underwent incisional biopsy of the oral lesion and were referred for a chest radiograph and then to the infectologist for treatment at the University Hospital of Maringá, state of Paraná, Brazil. Table 1 lists general data.

Paracoccidioidomycosis

Among the patients diagnosed with PCM ($n = 31$), 90.32% were men ($n = 28$; 28-69 years; mean 47.21 years); 18 (58.06%) were Caucasian, 12 (38.71%) melanoderma and in one case (3.23%), this information was missing. The majority of patients worked in agriculture ($n = 15$; 48.38%) and other occupations included drivers ($n = 4$; 12.90%), bricklayers ($n = 3$; 9.67%). Retirees ($n = 2$; 6.45%) and missing information ($n = 7$; 22.58%) completed the sample. The lesions were often multiple, with the jugal mucosa ($n = 13$; 25.49%) and alveolar ridge ($n = 12$; 23.52%) affected in most cases (Figure 1). In two (23.52%) patients, there was a diffuse lip enlargement.

The age range of patients found in our analysis was 28-69 years, with an average of 46.9 years.

Histoplasmosis

Of the three male patients (50-55 years; mean: 52.67 years) diagnosed with histoplasmosis, two (66.66%) were melanoderma and in one case (33.33%), the information was missing. Regarding the profession, one (33.33%) was a rural worker, one (33.33%) was a bricklayer and one (33.33%) was a mechanic. Again, multifocal involvement was frequent, and the palate, jugal mucosa and alveolar ridge were affected (Figure 2). All patients were immunocompetent.

Discussion

We report the experience of 25 years in a reference service in the diagnosis and treatment of oral lesions in southern Brazil. Epidemiological studies represent an important tool for the design of risk factors for a disease in a population. It is known that habits, ethnicity, geographical position and socioeconomic situation are some of the factors that influence the incidence of various diseases. In particular, SFI are endemic, emphasizing the importance of knowing their risk groups and clinical characteristics. Moreover, the socioeconomic impact caused by these diseases can be remarkable, adding to the serious and potentially fatal course of some cases.

Table 1. Collected data from patients.

Patient	Age	Gender	Ethnicity	Occupation	Site	Histopathological Diagnosis	Treatment
1	42	M	Caucasian	Farmer	Jugal mucosa	PCM	Referred to infectologist
2	45	F	Melanoderma	Farmer	Lip	PCM	Referred to infectologist
3	42	M	Caucasian	Driver	Alveolar ridge	PCM	Referred to infectologist
4	48	M	Caucasian	Other	Lip, jugal mucosa and tongue	PCM	Referred to infectologist
5	28	M	Caucasian	Bricklayer	Jugal mucosa and lip	PCM	Referred to infectologist
6	68	M	Caucasian	Driver	Tongue and lip	PCM	Referred to infectologist
7	40	M	Melanoderma	Driver	Alveolar ridge, jugal mucosa and palate	PCM	Referred to infectologist
8	54	M	Caucasian	Other	Alveolar ridge	PCM	Referred to infectologist
9	51	M	Melanoderma	Farmer	Alveolar ridge	PCM	Referred to infectologist
10	43	F	Caucasian	Other	Palate	PCM	Referred to infectologist
11	69	M	Melanoderma	Retiree	Jugal mucosa, lip and alveolar ridge	PCM	Referred to infectologist
12	53	M	Caucasian	Farmer	Jugal mucosa	PCM	Referred to infectologist
13	47	M	Melanoderma	Farmer	Alveolar ridge and floor of mouth	PCM	Referred to infectologist
14	48	M	Caucasian	Farmer	Lip	PCM	Referred to infectologist
15	50	M	Caucasian	Farmer	Jugal mucosa	PCM	Referred to infectologist
16	41	M	Caucasian	Bricklayer	Jugal mucosa, lip and floor of mouth	PCM	Referred to infectologist
17	38	M	Caucasian	Farmer	Floor of mouth and tongue	PCM	Referred to infectologist
18	45	M	Melanoderma	Farmer	Alveolar ridge	PCM	Referred to infectologist
19	28	M	Caucasian	Farmer	Palate	PCM	Referred to infectologist
20	45	M	Caucasian	Farmer	Jugal mucosa	PCM	Referred to infectologist
21	43	M	Caucasian	Other	Jugal mucosa	PCM	Referred to infectologist
22	45	M	Melanoderma	Other	Alveolar ridge, jugal mucosa, floor of mouth and palate	PCM	Referred to infectologist
23	49	M	Caucasian	Driver	Jugal mucosa and palate	PCM	Referred to infectologist
24	44	F	Caucasian	Other	Alveolar ridge	PCM	Referred to infectologist
25	50	M	Melanoderma	Mechanic	Alveolar ridge	Histoplasmosis	Referred to infectologist
26	53	M	N.I	Bricklayer	Palate	Histoplasmosis	Referred to infectologist
27	35	M	Caucasian	Other	Palate	PCM	Referred to infectologist
28	45	M	Melanoderma	Bricklayer	Lip, palate and alveolar ridge	PCM	Referred to infectologist
29	65	M	Melanoderma	Retiree	Alveolar ridge	PCM	Referred to infectologist
30	52	M	Melanoderma	Farmer	Tongue	PCM	Referred to infectologist
31	42	M	Melanoderma	Farmer	Alveolar ridge	PCM	Referred to infectologist
32	54	M	Melanoderma	Farmer	Jugal mucosa	PCM	Referred to infectologist
33	55	M	N.I	Farmer	Tongue, floor of mouth and palate	PCM	Referred to infectologist
34	55	M	Melanoderma	Farmer	Palate and jugal mucosa	Histoplasmosis	Referred to infectologist

F: female; M: male; N.I: not informed; PCM: paracoccidioidomycosis.

There are two varieties of SFI: opportunistic (systemic candidiasis, aspergillosis and mucormycosis) and respiratory endemic mycoses (histoplasmosis, blastomycosis, coccidioidomycosis, PCM and cryptococcosis) (Carrasco-Zuber et al., 2016). Of these, only PCM and histoplasmosis were found in this study. All cases of candidiasis were superficial (pseudomembranous and erythematous).

PCM or South American Blastomycosis, caused by the dimorphic fungus *P. brasiliensis*, mainly affects the lungs and can involve other organs by hematogenous route, such as lymph nodes, skin and oral mucosa (Godoy & Reichart, 2003; Trindade et al., 2017; Dutra et al., 2018). Transmission occurs through inhalation of the fungus, which reaches the pulmonary alveoli (primary site of infection), where the conditions are adequate for it to begin its transition to the yeast phase (Godoy & Reichart, 2003; Marques, 2010; Dutra et al., 2018;). Frequently, the oral mucosa is affected, being the primary clinical manifestation in many patients (Trindade et al., 2017).

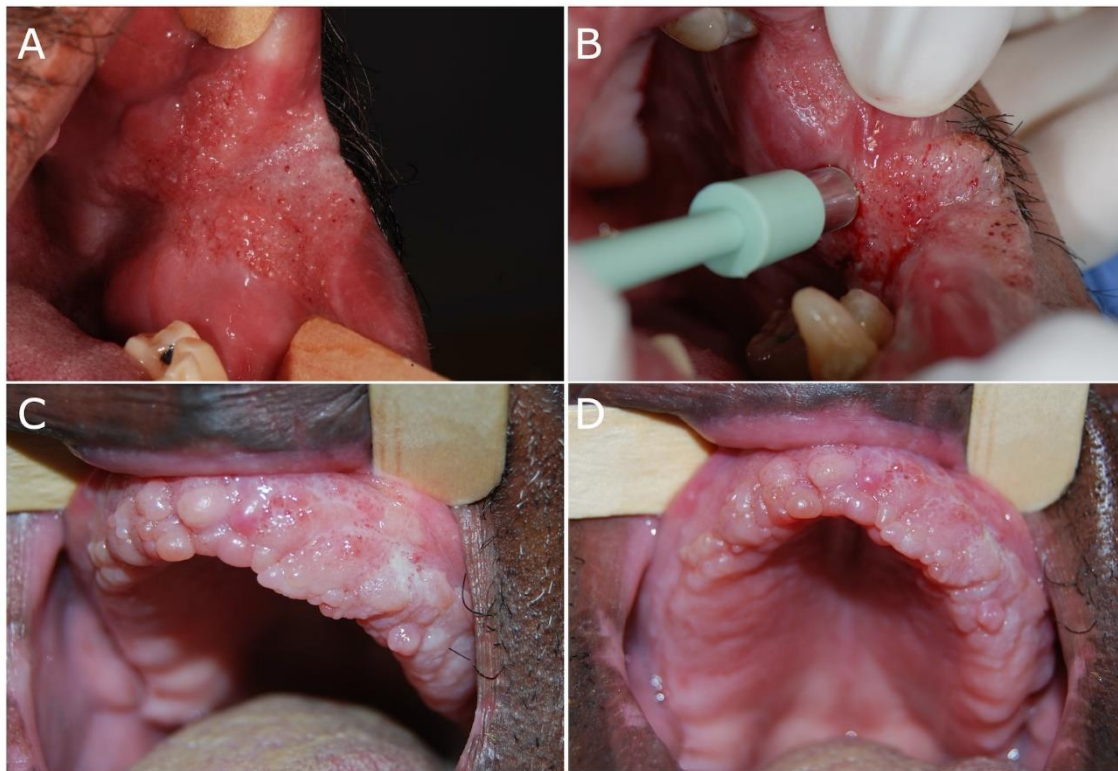


Figure 1. 48 years-old man, driver, melanoderma with asymptomatic diffuse mulberry lesions (moriform stomatitis) on the jugal mucosa (A), lips and upper alveolar ridge; incisional biopsy (B) confirmed the diagnosis of PCM. 59 years-old man, rural worker, melanoderma with symptomatic diffuse moriform lesions on the alveolar ridge (C, D).

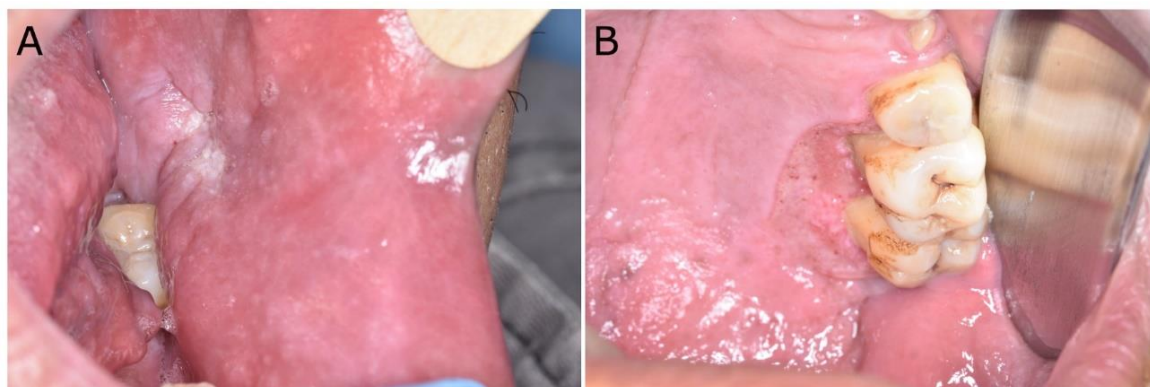


Figure 2. 56 years-old man, bricklayer, melanoderma with swelling and diffuse lesions on the jugal mucosa (A), and palate (B). Incisional biopsy (B) confirmed the diagnosis of histoplasmosis.

PCM is a rare disease in the world; it is endemic and acquired exclusively in Latin America, with the highest prevalence in South America (Trindade et al., 2017). *P. brasiliensis* has a geographic distribution limited to tropical and subtropical rural areas, from southern Mexico to parallel 32-34°S in Argentina and Uruguay (Tracogna et al., 2019). In Brazil, the most affected regions are the Southeast, Midwest and South. A second endemic area is located along the eastern border of the Amazon region (Martinez, 2015) and a third hyper-endemic area most recently installed in the western Amazon region (Martinez, 2017). The region where the present study was carried out is in southern Brazil, where agriculture is an important activity, being within the known endemic area of the country.

PCM mainly affects adult men, especially farm/rural workers or people who, at some point, were involved with the rural environment (Sposto et al., 1993; Bicalho et al., 2001; Godoy & Reichart, 2003; Paniago et al., 2003; Verli, Marinho, Souza, Figueiredo, & Yurgel, 2005; Brazão-Silva et al., 2011; Azenha, Caliento, Brentegani, & Lacerda, 2012; Barbosa de Paulo, Faria, & Durighetto Jr., 2014; López-Martínez et al., 2014; Souza, Jorge, & Xavier, 2014; Martinez, 2017; Trindade et al., 2017; Dutra et al., 2018), corroborating the present findings, with 90.32% of cases in men, almost half of rural workers (48.38%). In general, PCM reaches

a wide age group, from children to the elderly, but the prevalence is higher between the third and sixth decades of life (Martinez, 2017). The age range of patients found in our analysis was 28–69 years, with an average of 46.9 years. Some studies have found similar results, with greater involvement in the fourth decade of life (Spoto et al., 1993; Bicalho et al., 2001; Paniago et al., 2003; Verli et al., 2005; Brazão-Silva et al., 2011; Trindade et al., 2017). The ethnic predisposition for the development of PCM is still not well established (Martinez, 2017), although some studies (Bicalho et al., 2001; Trindade et al., 2017) corroborate our results where the majority of patients were Caucasian.

PCM most often affects the soft palate, gingiva, lower lip, jugal mucosa and tongue (Marques, 2010). In our study, single and multiple lesions were found, in which the jugal mucosa (25.49%) and the alveolar ridge (23.52%) were the most affected sites. Godoy and Reichart (2003) found the most affected sites were gingiva (76%) and tongue (71%). Trindade et al. (2017) found that jugal mucosa (31.82%) was the most affected site for single lesions and the lip (19.23%) for multiple lesions. For Bicalho et al. (2001) and Verli et al. (2005), the alveolar ridge and the gingiva were the most affected sites, with 51 and 63.9% cases, respectively.

Histoplasmosis, caused by the fungus *H. capsulatum*, affects the lungs and rarely affects the oral mucosa (O'Sullivan, Whitby, Chahoud, & Miller, 2004). Transmission and infection occur through aerosolization and inhalation of spores, and the soil contaminated with bird and bat droppings is the main environmental reservoir of this fungus (Telles, Karki, & Marshall, 2017; Bauddha, Jadon, Mondal, Vikarm, & Sood, 2018). It most often manifests as an acute lung infection that can progress to chronic pulmonary histoplasmosis or the disseminated form of the disease (Ferreira & Borges, 2009). Oral lesions are present in 30% to 50% patients with disseminated histoplasmosis (Akin, Herford, & Cicciù, 2011), which generally occurs in severely immunocompromised patients (Iqbal, Schifter, & Coleman, 2014). This serious opportunistic infection in association with HIV has assumed considerable importance and disseminated histoplasmosis is inserted in the spectrum of *AIDS-defining* diseases (Economopoulou et al., 1998). In these cases, this respiratory condition may be fatal.

Histoplasmosis is more commonly found in the United States (Neville et al., 2016; Folk & Nelson, 2017); however, it also affects some regions of Central and South America, Africa, Asia and Australia (O'Sullivan et al., 2004; Folk & Nelson, 2017; Singh et al., 2019). In Brazil, although cases of histoplasmosis have been underestimated, it is believed that this mycosis is an important health problem (Valle et al., 2006), and that it is endemic to the country (Fava & Fava Netto, 1998). A recent systematic review (Almeida, Almeida-Silva, Guimarães, Almeida-Paes, & Zancopé-Oliveira, 2019) showed that the Northeast, Midwest, Southeast and South regions are the most affected, which again includes the region where the present study was developed.

Corroborating our findings, most studies show that histoplasmosis mainly affects men (Economopoulou et al., 1998; Couppié et al., 2002; Ferreira, Cardoso, Borges, Ferreira, & Loyola, 2002; Singh et al., 2019; Lv, Jiang, He, Li, & Meng, 2020). However, regarding ethnicity there are some discrepancies among studies. Economopoulou et al. (1998) observed a higher occurrence in Caucasian (33.3%), whereas Ferreira et al. (2002) reported that 90% patients were melanoderma. In our analysis, 66.66% patients were melanoderma. Although oral lesions occur more commonly in immunosuppressed patients (Iqbal et al., 2014), in the present study, all cases were immunocompetent individuals, with the palate being the most affected site. According to the literature, tongue, palate, jugal mucosal and gingiva are commonly affected (Scully & Almeida, 1992; Economopoulou et al., 1998; Couppié et al., 2002; Ferreira et al., 2002; Valle et al., 2006).

For both mycoses, the treatment depends on the severity of the disease and is carried out by the infectologist. The dentist has an essential role in the recognition of the disease, whose oral manifestations may be the first sign. In this context, the performance of the biopsy is essential, since the microscopic examination confirms the diagnosis. It is also important to emphasize that, especially in patients with histoplasmosis, immunosuppressive conditions should be investigated, such as the HIV virus. For mild and moderate cases of PCM, itraconazole is the drug of choice (Marques, 2010). Other alternatives include trimethoprim-sulfamethoxazole and voriconazole (Marques, 2010). For severe cases, amphotericin B deoxycholate is used (Marques, 2010). For chronic pulmonary histoplasmosis and mild to moderate disease, itraconazole is the most indicated medication (Marques, 2010). In progressive disseminated or severe disease, amphotericin B is adopted, followed by the use of itraconazole (Marques, 2010). Posaconazole has been used as a rescue treatment for severe forms of histoplasmosis, when patients are intolerant to standard therapy or have refractory disease (Marques, 2010). In patients with AIDS, even with advances in antifungal therapy, mortality and morbidity from SFI have not changed significantly in the last years. Furthermore, long-term exposure to antifungal drugs (e.g. fluconazole) has led to the development of resistance in 6% to 36% cases

(Vidya, Rao, Nittayananta, Liu, & Owotade, 2016). The development of new antifungal therapeutic agents and the use of alternative therapies appears to be urgent, as well as new effective strategies to enhance the host immune status (Vidya et al., 2016). In all cases of the present study, after clinical and microscopic diagnosis, patients were referred for systemic treatment, reinforcing the importance of the dentist in recognizing the disease through its oral manifestations.

Conclusion

In short, systemic fungal infections should be included in the differential diagnosis in patients from endemic areas. In addition, the inevitable human mobility and globalization make knowledge of these mycoses necessary worldwide, especially because advanced cases in immunocompromised patients can be fatal. This requires training for clinical suspicion and application of all available tools to obtain early diagnosis, reducing morbidity, socioeconomic impact and mortality.

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