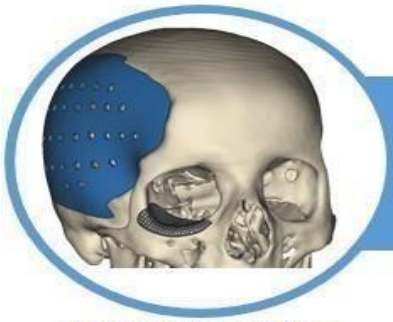

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Epidemiological aspects and oral implications of Paracoccidioidomycosis infection: an integrative review.

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INTEGRATIVE REVIEW

ABSTRACT

Paracoccidioidomycosis (PCM) is a systemic mycosis caused by the dimorphic fungus Paracoccidioides brasiliensis. It represents a significant infection in South America, occurring mainly in tropical and subtropical countries such as Brazil. Oral mucosal lesions, which are the most important symptom in dentistry, may be the first visible physical manifestation of the disease, often preceding even pulmonary lesions. This study aims to carry out an integrative literature review to identify the main epidemiological aspects and oral implications of Paracoccidioidomycosis (PMC) infection. A search was carried out in the PubMed, LILACS and SciELO databases and, after applying the inclusion, exclusion, eligibility and thematic relevance criteria, 18 articles were selected for analysis in this study. Paracoccidioidomycosis (PCM) is endemic in Brazil and mainly affects middle-aged and elderly men and occurs in rural areas. It is a systemic disease where clinical manifestations are often added to oral lesions. Dentists play a key role in identifying these lesions, in the correct diagnosis and treatment of this disease. Making PCM notification compulsory in Brazil is essential.

Keywords: Paracoccidioidomycosis, Epidemiology, Oral lesions, Dentistry.

Aspectos epidemiológicos e implicações orais da infecção por Paracoccidioidomycosis: uma revisão integrativa

RESUMO

A Paracoccidioidomicose (PCM) é uma micose sistêmica causada pelo fungo dimórfico Paracoccidioides brasiliensis. Representa uma infecção significativa na América do Sul, ocorrendo principalmente em países tropicais e subtropicais como o Brasil. As lesões da mucosa oral, que são os sintomas mais importantes na odontologia, podem ser a primeira manifestação física visível da doença, muitas vezes precedendo até mesmo as lesões pulmonares. Este estudo tem como objetivo realizar uma revisão integrativa da literatura para identificar os principais aspectos epidemiológicos e implicações orais da infecção por Paracoccidioidomicose (PMC). Foi realizada busca nas bases de dados PubMed, LILACS e SciELO e, após aplicação dos critérios de inclusão, exclusão, elegibilidade e relevância temática, foram selecionados 18 artigos para análise neste estudo. A paracoccidioidomicose (PCM) é endêmica no Brasil e acomete principalmente homens de meia-idade e idosos e ocorre em áreas rurais. É uma doença sistêmica onde muitas vezes as manifestações clínicas se somam às lesões orais. Os dentistas têm um papel fundamental na identificação destas lesões, no correto diagnóstico e tratamento desta doença. Tornar a notificação do PCM compulsória no Brasil é essencial.

Palavras-chave: Paracoccidioidomicose, Epidemiologia, Lesões orais, Odontologia.

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INTRODUCTION

Paracoccidioidomycosis (PCM) is a systemic mycosis caused by the dimorphic fungus Paracoccidioides brasiliensis. It represents a significant infection in South America, occurring mainly in tropical and subtropical countries such as Brazil, Venezuela, Argentina and Colombia [1]. Brazil is considered an endemic country, with a higher prevalence of PCM in the South, Southeast and Midwest regions [2].

The microorganism first enters the human body through nasal inhalation of the fungus. Once present in the pulmonary alveoli, the primary site of infection, the temperature of the human body (37°C) provides the right conditions for infection, allowing the fungus to initiate its dimorphic transition to its yeast form. From the lungs, it can spread to various organs and systems via lymphatic and hematogenous routes, causing secondary lesions [3]. Oral mucosal lesions, which are the most important symptom in dentistry, may be the first visible physical manifestation of the disease, often preceding even pulmonary lesions [4].

This study aims to carry out an integrative literature review to identify the main epidemiological aspects and oral implications of Paracoccidioidomycosis (PMC) infection.

METHODOLOGY

This is an integrative review of the literature of the qualitative type, which is a type of research that enables the search and knowledge on related subjects and the list of opinions of different authors to find answers about the intended objective. This study was based on the following guiding question: What are the main epidemiological aspects and oral implications of Paracoccidioidomycosis infection?

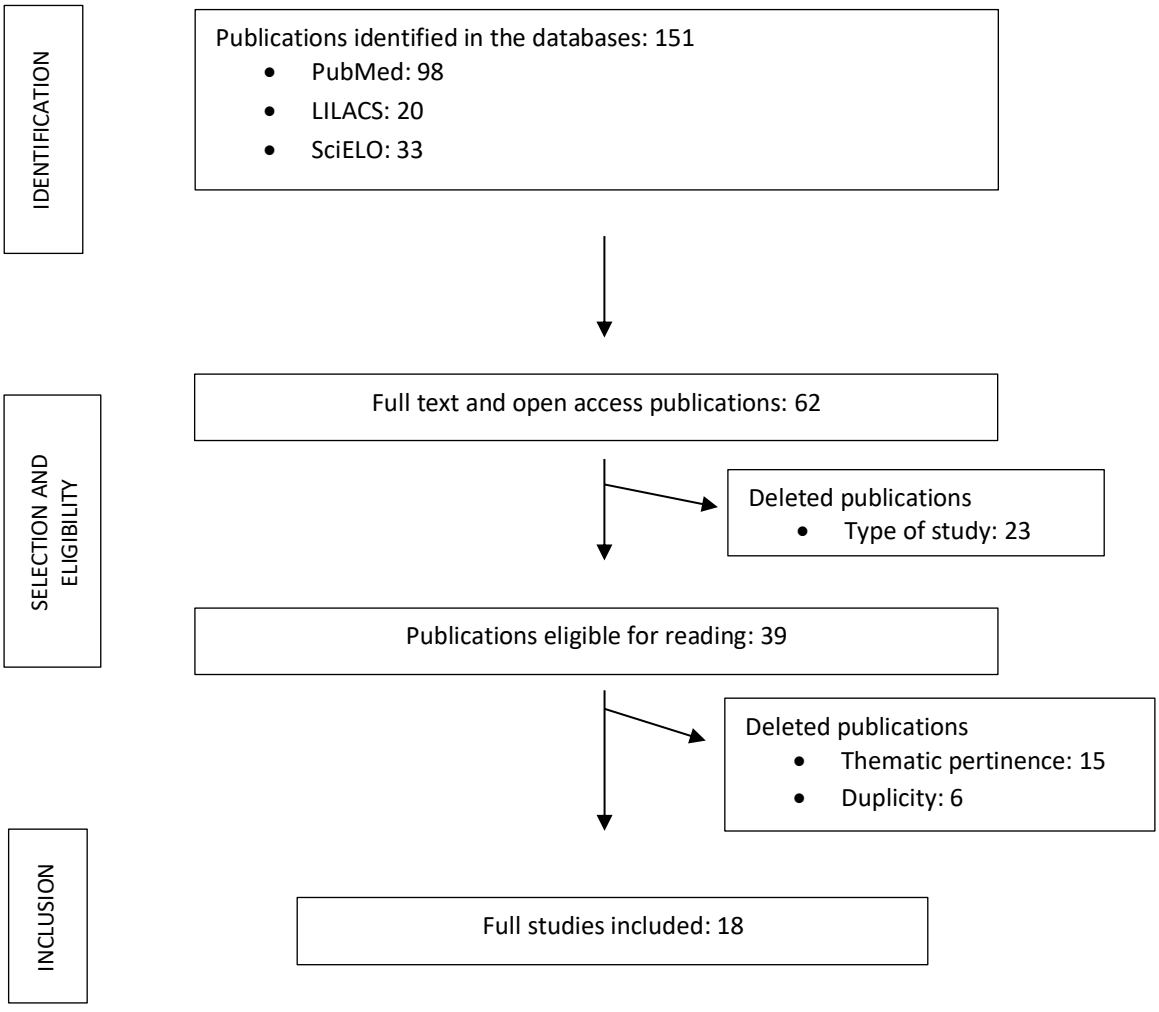
The search was carried out in the PubMed, LILACS and SciELO databases, using the health descriptors “Paracoccidioidomycosis”, “Dentistry” and “Oral”, with the help of the Boolean operator “and” being used as follows: (“Paracoccidioidomycosis” and “Oral”) and (“Paracoccidioidomycosis” and “Dentistry”). Databases gather and organize bibliographic references in a structured way that allow their recovery by interested users”. This was carried out from May to July 2023.

Inclusion criteria were a study published in the last 10 years (2013-2023), available free of charge, in Portuguese, English and Spanish. Articles that did not follow the eligibility criteria and that did not address relevant data for the present study were excluded. Those that are just the summary were also excluded; duplicate articles; studies that have not been approved by a research ethics committee; systematic, systematized, integrative and meta-analysis review articles; studies not related to dentistry.

RESULTS

In all, 151 publications were retrieved, after careful reading and application of the eligibility criteria, twenty articles were included in this review (Figure 1).

Figure 1. Flowchart of the article selection process for the integrative review.



Source: Authorship, 2023.

Initially, from the search by combining the descriptors “Paracoccidioidomycosis” and “Oral”, 68 articles were obtained in the PubMed database, 18 articles in the LILACS database and 33 articles in the SciELO database. Using the combination of the descriptors “Paracoccidioidomycosis” and “Dentistry”, 30 articles were obtained in the PubMed database, 2 articles in the LILACS database and no articles were found in the SciELO database.

These were analyzed by reading the titles and abstracts, thus selecting 18 articles. To facilitate understanding, the articles in question were placed in Table 1 containing the author, title, year of publication, journal and objective of the study.

Table 1: Summary table of the analyzed publications.

Nº	Author/Year	Title	Journal	Objective
1	DE DE OLIVEIRA *et al.* (2023)	Oral paracoccidioidomycosis: a retrospective study of 95 cases from a single center and literature review.	Medicina Oral, Patologia Oral y Cirugia Bucal	Report the clinicopathological features of individuals diagnosed with oral PCM lesions at an oral and maxillofacial pathology service in Rio de Janeiro, Brazil.
2	COSTA *et al.* (2019)	A Brazilian male with typical oral and pulmonary paracoccidioidomycosis.	Medical Journal of the Islamic Republic of Iran	Enhance the awareness of generalists about this mycosis.
3	SOUZA *et al.* (2019)	Oral paracoccidioidomycosis in a non-endemic region from Brazil: A short case series.	Journal of Clinical and Experimental Dentistry	Evaluate the clinicopathologic features of a case series of oral PCM in a non-endemic region from Brazil (Northeastern region), discussing the clinical and histopathological differential

				diagnoses of the oral manifestations of the disease.
4	DUTRA *et al.* (2018)	Oral paracoccidioidomycosis in a single-center retrospective analysis from a Brazilian southeastern population.	Journal of Infection and Public Health	Trace the epidemiological and clinical profiles of patients with oral lesions treated at the University Hospital Cassiano Antonio Moraes, Federal University of Espirito Santo.
5	ARIAS RAMOS *et al.* (2021)	Thinking in paracoccidioidomycosis: a delayed diagnosis of a neglected tropical disease, case report and review of clinical reports and eco-epidemiologic data from Colombia since the 2000.	BMC Infectious Diseases	Report a case of a patient with Chronic Multifocal Paracoccidioidomycosis with long-standing symptoms and a delayed diagnosis caused by several barriers to achieve it.
6	WEBBER *et al.* (2014)	Disseminated paracoccidioidomycosis diagnosis based on oral lesions.	Contemporary Clinical Dentistry	Present a case report of PCM with lung, skin and oral manifestations whose diagnosis was reached based mainly on oral lesions, by the dentist.

7	ALBUQUERQUE NETO *et al.* (2018)	Diagnosis and Treatment of Paracoccidioidomycosis in the Maxillofacial Region: A Report of 5 Cases.	Case Rep Otolaryngol.	Report five cases of para-coccidioidomycosis in the facial region, diagnosed and treated in a hospital in the countryside of São Paulo, Brazil.
8	ALVARADO *et al.* (2021)	Epidemiology of paracoccidioidomycosis in Venezuela: a retrospective study from 1954 to 2019.	Mem Inst Oswaldo Cruz	To document the epidemiology of Paracoccidioidomycosis in Venezuela.
9	DE SOUZA; JORGE; XAVIER (2014)	Paracoccidioidomycosis in southern Rio Grande do Sul: a retrospective study of histopathologically diagnosed cases.	Braz J Microbiol.	To perform a retrospective analysis of the Paracoccidioidomycosis cases in the countryside south of Rio Grande do Sul, Brazil.
10	DOS SANTOS *et al.* (2017)	Chronic paracoccidioidmycosis in a woman with Crohn Disease.	Dermatol Online J.	To report a rare case of chronic paracoccidioidomycosis in a woman with Crohn disease in the setting of treatment with azathioprine and mesalazine.
11	MOTA *et al.* (2019)	An autochthonous case of	Rev	To describe a new autochthonous case of paracoccidioidomycosis from

		paracoccidioidomycosis in a new area of Ceara State, Northeastern Brazil.	Inst Med Trop Sao Paulo.	a distinct area of Ceara and review the characteristics of paracoccidioidomycosis occurrence in Northeastern Brazil.
12	VALE *et al.* (2022)	Paracoccidioidomicose afetando a mucosa bucal: relato de caso - Paracoccidioidomycosis affecting the buccal mucosa: case report - Paracoccidioidomicosis con afectación de la mucosa oral: relato de caso.	Rev. cir. traumatol. buco-maxilo-fac.	To report the case of a 53-year-old rural worker with PCM in the oral mucosa, emphasizing the importance of the dental surgeon in recognizing oral lesions and performing a biopsy for the diagnosis and proper management of this disease.
13	HENSCHEL *et al.* (2022)	Oral manifestations of systemic fungal infections: 25-year experience in an endemic region.	Acta sci.	To report the prevalence and characteristics of oral lesions in patients diagnosed with systemic fungal infections over a 25-year period in southern Brazil.
14	MARIO *et al.* (2020)	Paracoccidioidomycosis in the northern region of Rio Grande do Sul.	Rev. epidemiol. controle infecç.	To perform a retrospective analysis of Paracoccidioidomycosis cases from the northern region of Rio Grande do Sul, Brazil.

15	MERINO-ALADO *et al.* (2018)	Oral Manifestations Associated to Paracoccidioidomicosis and Histoplasmosis.	Pesqui. bras. odontopediatria clín. Integr.	To determine the frequency and clinical forms of oral manifestations associated to Paracoccidioidomycosis and Histoplasmosis.
16	VOLPATO *et al.* (2016)	Spatial Distribution of Cases of Paracoccidioidomycosis With Oral Manifestations in The State of Mato Grosso, Brazil.	Rev. Odontol. Bras. Central.	To analyze the spatial distribution of cases of paracoccidioidomycosis with oral manifestations in the state of Mato Grosso using georeferencing.
17	PEREIRA MACEDO *et al.* (2014)	Paracoccidioidomycosis in oral cavity: case report.	Odontol. clín.	To report case of paracoccidioidomycosis, highlighting the importance of Hospital Dentistry for their diagnosis.
18	GORDÓN-NÚÑEZ *et al.* (2014)	Recurrent Oral Manifestations of Paracoccidioidomycosis without Pulmonary Involvement: Case Report and Review of Literature.	Int. J. odontostomatol.	To describe a case of recurrence of chronic paracoccidioidomycosis 11 years following the initial diagnosis.

Source: Authorship, 2023.

DISCUSSION

Paracoccidioidomycosis (PCM) is a systemic mycosis typical of Latin America with

a wide range of clinical manifestations that can affect any susceptible host, being considered endemic in Brazil, Venezuela, Colombia, Ecuador and Argentina. The characteristic climate of the Latin American region creates suitable conditions not only for Paracoccidioides spp., but also for other dimorphic fungi that cause systemic mycoses. Thus, it is fundamental to consider this agent in the diagnosis of granulomatous diseases. It is important to highlight that this mycosis is not considered a notifiable disease, despite being associated with a significant morbidity and mortality rate in underdeveloped countries [5, 6].

A study indicates that a large number of patients with PCM (65.2%) were involved in agricultural activities. Agricultural activities predispose individuals to mycosis due to greater exposure to infectious fungal propagules. Although early diagnosis and immediate referral of the patient for treatment are important factors in reducing the number of complications caused by this disease, a study indicates a long period of time between the onset of clinical symptoms and the diagnosis. This delay may be related to the difficulty of health professionals in making an accurate diagnosis of PCM based on early lesions, as well as rural patients who wait longer before seeking professional help. In addition, the long period between the onset of symptoms and diagnosis can also be attributed to the lack of access to health services [7].

The geographic distribution of Paracoccidioides spp. it is predominantly limited to certain regions of North, Central and South America, characterized by highly humid climates and mild temperatures. In Brazil, studies indicated that the chronic form was found more frequently in adult men and rural workers. The male/female ratio varies according to geographic region, from 3:1 to 10:1 in the Southeast and Midwest regions of Brazil, respectively. Although PCM is uncommon and often overlooked in Northeastern Brazil, it should be considered mainly in male adults and farmers with pulmonary or chronic mucosal lesions. It is noteworthy that human migration, the expansion of agricultural frontiers, climate and environmental changes and new agricultural and social practices have been impacting the occurrence of Paracoccidioides spp., a fact that may help explain the identification of new areas with the presence of the fungus [8, 9].

PCM is rare in northeastern Brazil. Despite this, this deep mycosis presents

epidemiological and clinical characteristics similar to those observed in endemic regions of Brazil, affecting mainly adults between 30 and 60 years old, men, people involved in rural activities and residents in rural areas. Oral manifestations include multiple, ulcerated, erythematous or granular lesions, preferentially affecting the buccal mucosa, soft and hard palate and gingiva. Thus, professionals should be aware of the clinical characteristics of PCM, since oral manifestations are usually the first clinical sign of the disease. PCM should be considered in the differential diagnosis of chronic mouth ulcers, whether they are unique or mainly those that develop multiple [10, 11].

PCM has a significant medical and social impact in the most endemic areas. Considering that oral ulceration can be one of the first signs in patients with PCM, the description of these clinical manifestations provides important data for early diagnosis. The most widely used diagnostic methods included direct mycological and histopathological examinations. In addition to oral lesions, the most common signs and symptoms are weight loss, dyspnea and cough. The earlier the diagnosis, the smaller the consequences, especially the respiratory ones, which can lead to incapacity for work and poor quality of life [12].

Oral lesions caused by Paracoccidioidomycosis (PCM) usually appear in single or multiple forms as “mulberry-like” ulcerations that most commonly affect the gingiva/alveolar ridge, palate, lips/labral commissure and buccal mucosa. Study indicates that the proportional frequency of newly diagnosed cases of oral PCM has increased markedly in the last two decades (68.4%), mainly between 2020 and 2021. Lesions in the oral cavity are common findings in PCM, but they do not seem to be biopsied frequently. In Brazil, this may occur because patients with suspected PCM are referred for tertiary care, mainly due to the involvement of several organs and tissues. The epidemiology of oral PCM demonstrates a higher incidence in middle-aged or older male adults [13, 14].

Study indicates that PCM should become a notifiable disease in endemic countries. The hypotheses of imported cases of PCM should be considered in the differential diagnosis of migrant patients or with a history of work or tourism trips to an endemic region. Therefore, clinical practice around the world must gain basic knowledge about the classic features of this tropical mycosis [15].

The lack of new information in the last two decades on ecoepidemiology and the clinical and social characterization of patients with Paracoccidioidomycosis reaffirms it as a neglected tropical disease, a situation that has worsened in the last two decades despite the computer age, and is also an appeal for physicians to, institutions and government start working on this issue again. The main problems in recognizing PCM seem to be 1) the apparent rare occurrence of the disease; 2) the difficulty of diagnosing the disease in a timely manner; 3) clinicians' lack of interest in making it more visible, from health system instances to individual medical education instances. From this perspective, it seems that the way to start solving this problem may be the creation of a national network involving leaders from different medical schools [16].

PCM is a systemic, non-contagious mycosis acquired from soil contaminated with microorganisms. It often presents oral manifestations and occasional skin lesions. Therefore, dentists must be able to recognize its clinical features in order to establish an accurate diagnosis. Although PCM is a well-known disease, there are reports whose diagnosis is difficult and time-consuming. This delay can be explained by the fact that the symptoms of the pulmonary manifestations are nonspecific, and the clinical picture evolves slowly, as the skin lesions are not properly diagnosed. In most cases, the diagnosis is not reached until approximately 3-5 months [17].

Paracoccidioidomycosis represents an important public health problem due to its high potential for morbidity and mortality. Long and expensive treatments, in addition to recurrent episodes, require innovations in the treatment of PMC. It should be considered as a differential diagnosis in cases of opportunistic infection in immunosuppressed patients [18]. Studies report a variety of presentations of the same infection, from complicated cases to cases that do not classically present as PMC [19, 20].

In countries where PCM and histoplasmosis are endemic mycoses, the dentist should be highly suspicious of patients with oral lesions and always look for epidemiological clues to include a rigorous assessment of general health conditions during the examination. This is sometimes neglected by a significant number of dentists, who are important professionals in the diagnosis of both mycoses, as patients often seek care for oral lesions and not respiratory symptoms, erroneously associated with

smoking. An adequate mycological examination of the lesions is a fundamental tool to reach the diagnosis and avoid the torpor evolution of these diseases. In addition, dentists must have the ability to suspect and diagnose HIV/AIDS and other immunosuppressive diseases in patients with oral manifestations of PCM and histoplasmosis [21].

Clinical dental examination to detect oral lesions is important for the diagnosis of PCM. It is also recommended the continuous need for the Hospital Dentistry service, confirmed by the interaction of the Dental Surgeon with the other professionals from the different areas of health, being determinant for the integral care of the hospitalized patient [22].

CONCLUSION

In view of the above, it is inferred that Paracoccidioidomycosis (PCM) is a typical disease of the Latin American region, being endemic in Brazil and in other countries of South America, affecting mainly middle-aged, older men, occurrence in rural areas. It is a systemic disease where the clinical manifestations are often added to the oral lesions, which can develop serious sequelae if the diagnosis is late or the treatment is misguided. Thus, dentists play a fundamental role in the identification of these lesions, in the correct diagnosis and treatment of this disease.

It highlights the importance of making the clinical diagnosis of PCM compulsory notification in Brazil for the implementation of preventive measures and early diagnoses that can lead to more effective treatments and less sequelae for the population.

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