



The Brazilian Journal of INFECTIOUS DISEASES

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Original Article

Intestinal Paracoccidioidomycosis: Case report and systematic review

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ARTICLE INFO

Article history:

Received 13 May 2021

Accepted 29 July 2021

Available online 27 August 2021

Keywords:

Paracoccidioides
Inflammatory Bowel Diseases
Gastroenteritis
Inflammation
Amphotericin B
Colectomy
Mycoses

ABSTRACT

Background: Paracoccidioidomycosis is a systemic mycosis considered endemic and limited to Latin America with the majority of registered cases originating from Brazil. The purpose of this paper was to report a case of a female patient with paracoccidioidomycosis mimicking inflammatory bowel disease and to systematically review available cases of the intestinal presentation of this infectious disease.

Case report: Female patient, 32-years old, previously asymptomatic, presenting with acute pain in the lower right abdomen, associated with signs of peritoneal irritation and abdominal distension. Urgent surgery was performed, which identified a severe suppurative perforated ileitis. The anatomopathological study revealed fungal structures shaped as a ship's pilot wheel in Grocott-Gomori's staining, suggestive of *Paracoccidioides* spp.

Methods: Studies were retrieved based on Medical Subject Headings and Health Sciences Descriptors, which were combined using Boolean operators. Searches were run on the electronic databases Scopus, Web of Science, MEDLINE (PubMed), BIREME (Biblioteca Regional de Medicina), LILACS (Latin American and Caribbean Health Sciences Literature), SciELO (Scientific Electronic Library Online), Embase, and Opengray.eu. Languages were restricted to English, Spanish and Portuguese. There was no date of publication restrictions. The reference lists of the studies retrieved were searched manually. Simple descriptive analysis was used to summarize the results.

Results: Our search strategy retrieved 581 references. In the final analysis, 34 references were included, with a total of 46 case reports. The most common clinical finding was abdominal pain and weight loss present in 31 (67.3%) patients. Most patients were treated with itraconazole (41.3%) and amphotericin B (36.9%). All-cause mortality was 12.8%.

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<https://doi.org/10.1016/j.bjid.2021.101605>

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Conclusions: Paracoccidioidomycosis should be suspected in endemic areas, specially as a differential diagnosis for inflammatory bowel disease. Endoscopic tests and biopsy are useful for diagnosis and treatment with antifungal drugs seem to be the first treatment option to achieve a significant success rate.

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Introduction

Paracoccidioidomycosis (PCM) is a systemic mycosis considered endemic and limited to Latin America with the majority of registered cases originating from Brazil.¹ There are two species known to cause this disease: *P. brasiliensis* and *P. lutzii*.²

Currently, PCM is classified into two main clinical presentations including acute/subacute (juvenile type) and chronic (adult type) forms. Acute/subacute PCM is frequently observed in children and adults under 30 years old³ accounting for less than 10 percent of the cases. In this form, both men and women are affected equally. Symptoms and signs observed in this form include weight loss, fever, mild to moderate anemia, and enlargement of multiple lymph nodes. In addition, organs including the liver, spleen, bone marrow, and digestive tract may be affected.⁴

In contrast, the chronic form is more common and can represent a reactivation of the primary infection. It commonly affects men between 30 and 60 years of age who work in agriculture for a long time.³ PCM can disseminate to any part of the body via lymphatic or hematogenic route. In the adult-type disease, there might be pulmonary involvement and ulcerated lesions of the skin and mucosa (oral and nasal). Besides the mouth, other gastrointestinal portions are rarely affected. However, all segments may be involved. In these cases, intestinal PCM predominantly affects the jejunum, ileum, and proximal portions of the large intestine.⁵

PCM has been previously described as a condition that can mimic other diseases, especially Crohn's disease (CD), in patients from endemic countries.⁶ CD is a chronic inflammatory condition that can affect any part of the digestive tract. Clinical

manifestations of gastrointestinal involvement of PCM include abdominal pain, nausea, diarrhea, and colonoscopy findings such as deep ulcers and strictures are very similar to those of Crohn's disease.⁷ For this reason, PCM should be considered in the differential diagnosis of inflammatory bowel diseases, specially in endemic countries, such as Brazil.⁸

The purpose of this paper is to report a case of a female patient with intestinal PCM infection mimicking stricturing CD and to perform a systematic review of the available cases reported on gastrointestinal PCM infection.

Case report

A previously healthy and asymptomatic 32-year-old female patient sought care in the emergency department presenting with acute pain in the lower right abdomen, associated with signs of peritoneal irritation and abdominal distension. The oral cavity and skin were unremarkable. A computed tomography scan was suggestive of appendicitis. The chest radiograph was normal. The patient underwent urgent surgery, which identified a severe suppurative perforated ileitis. A right colectomy with ileocolonic anastomosis was performed. The anatomopathological study showed chronic granulomatous inflammation of the ileum, large intestine, and pericolic lymph nodes, without evidence of inflammatory bowel disease. Fungal structures shaped as a ship's pilot wheel in Grocott-Gomori's staining were identified, suggestive of *Paracoccidioides* spp. ileitis and colitis (Figure 1).

In the following two weeks, the patient presented vomiting, alternating diarrhea with constipation, and severe abdominal pain. An urgent colonoscopy was performed,

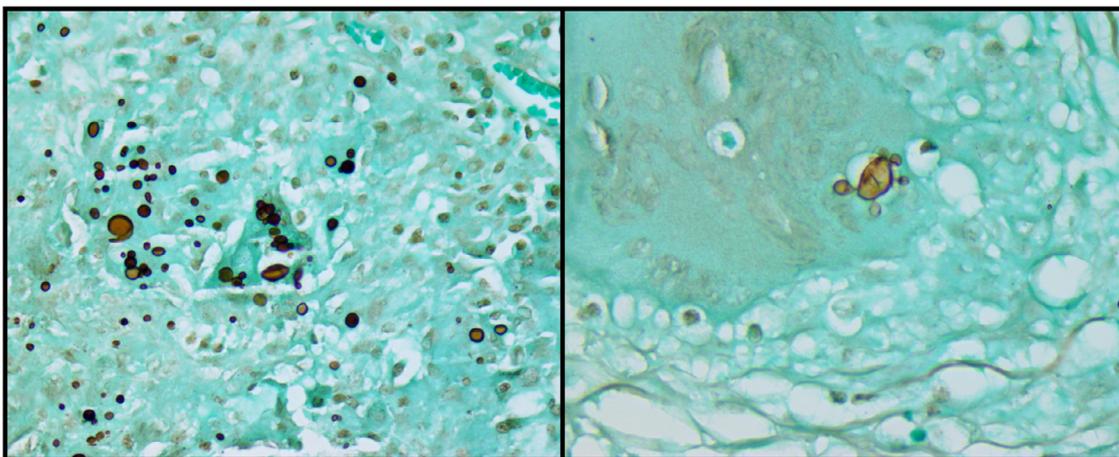


Figure 1 – Biopsy, ileum, (Grocott-Gomori. Immersion). Multi-budding fungal cell, shaped as a ship's pilot wheel, characteristic of the *Paracoccidioides* genus.



Figure 2 – Colonoscopy, descending colon. Strictureing ulcers caused by PCM infection.

which showed multiple colonic deep ulcers, which prevented the scope of reaching the ileo-colonic anastomosis (Figure 2). The anatomopathological study of biopsies was unspecific and staining for fungal structures was negative. At that time, she was started on amphotericin B deoxycholate 50 mg daily for 28 days according to her weight, with good improvement of symptoms. Afterward, she was kept on maintenance therapy with itraconazole 200 mg daily.

One month after ending the treatment with amphotericin B, a second colonoscopy was performed because of persistent abdominal pain, which showed a stricture in the left colon. A barium enema was performed, showing two short strictures (Figure 3). Endoscopic Balloon Dilation (EBD) was performed (Figure 4) with a mild short-lived improvement in symptoms. A few days after the second EBD, the patient presented to the emergency department with signs of bowel obstruction,



Figure 3 – Barium enema. Two small and narrow strictures in descending and transverse colon (circles).

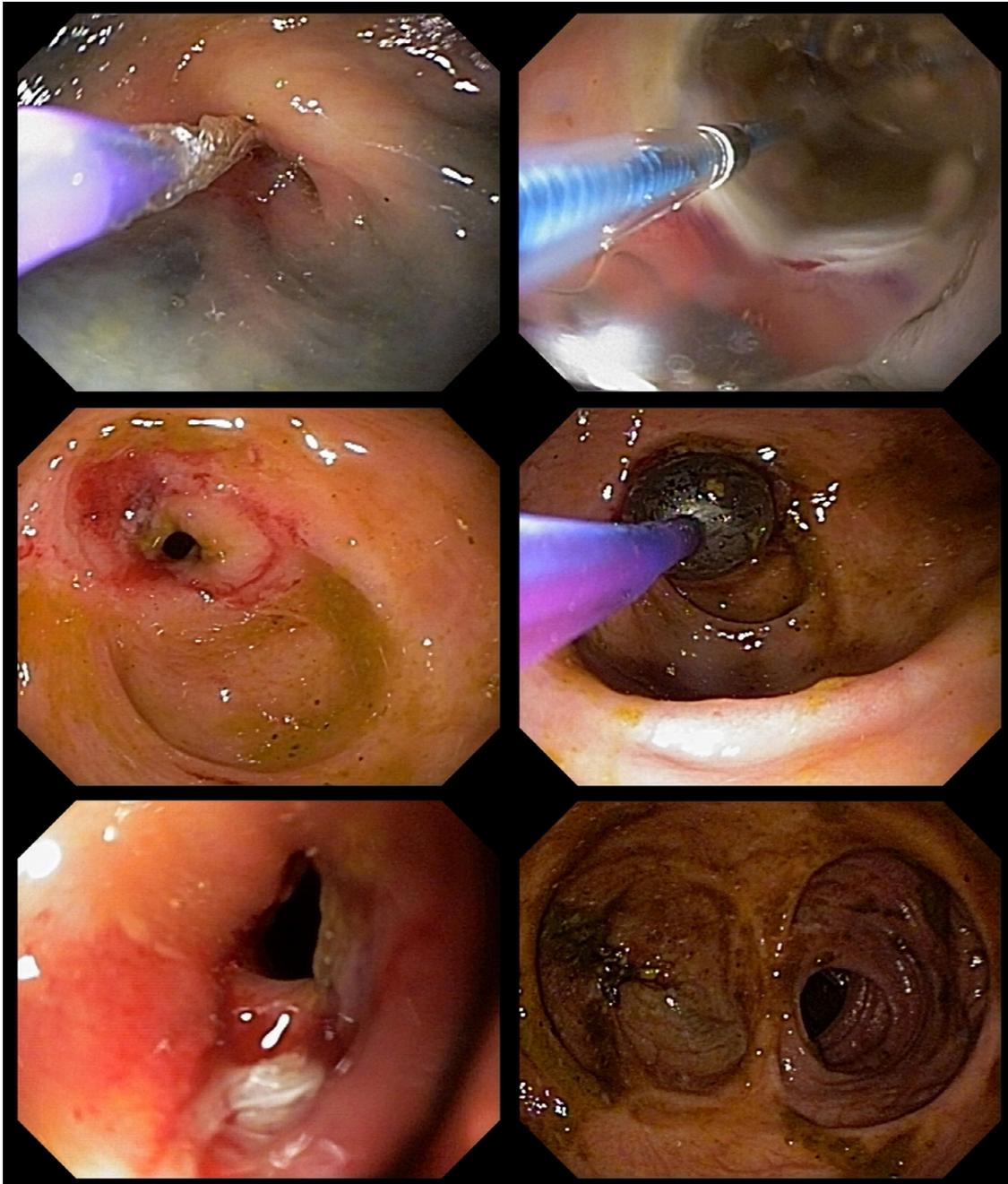


Figure 4– Colonoscopy, descending and transverse colon. Two narrow strictures, before and after endoscopic Balloon Dilation, and ileo-colonic anastomosis, free of strictures.

requiring an emergency total colectomy. The anatomopathological study was unspecific and staining for fungal structures was negative.

After the surgery, symptoms of the patient were resolved. She is currently using maintenance therapy with itraconazole, with a plan of completing 18 months of treatment.

Materials and methods

This study was carried out under the recommendations contained in the Preferred Reporting Items for Systematic

Reviews and Meta-Analysis (PRISMA) guidelines.⁹ Our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO), maintained by York University (CRD42021246015).

Data sources

Studies were retrieved using the terms described in [Appendix A](#). Searches were run in November 2020 on the electronic databases Scopus, Web of Science, MEDLINE (PubMed), BIREME (Biblioteca Regional de Medicina), LILACS (Latin American and Caribbean Health Sciences Literature), SciELO

(Scientific Electronic Library Online), Embase and Opengray. eu. References of included studies were screened for relevant records. There was no language or date of publication restrictions. The reference lists of the retrieved studies were submitted to manual search.

Inclusion criteria and outcomes

Case report or case series studies were eligible for selection. If there was more than one study published using the same case, the most recent study was selected for analysis. Studies published only as abstracts were included, as long as the data available made data collection possible. Studies written in languages other than English, Spanish or Portuguese were excluded.

Study selection and data extraction

An initial screening of titles and abstracts was the first stage to select potentially relevant papers. The second step was the analysis of the full-length papers. Two independent reviewers extracted data using a standardized form after assessing and reaching consensus on eligible studies. The same reviewers separately assessed each study and extracted data about the characteristics of the subjects and the outcomes measured. A third reviewer was responsible for clearing divergences in study selection and data extraction

Quality assessment

Methodological quality assessment of case reports and case series was performed by two independent authors using the tool presented by Murad et al.¹⁰ Divergences were discussed with a third reviewer until consensus was reached. Since questions 5 and 6 of the original tool are mostly relevant to cases of adverse drug events, we modified them to better suit the cases of paracoccidioidomycosis. Therefore, we considered question 5 as 'was there a response to the specific treatment for paracoccidioidomycosis?' and question 6 as 'was there a histological confirmation of the diagnosis?'

Statistical analysis

Simple descriptive statistics, such as the mean and Standard Deviation (SD), frequency, and median were used to characterize the data. Data were summarized using RStudio (version 4.0.2).

Results

Using the search strategy, 581 references were found and 224 references were excluded because they were duplicates. After analyzing titles and abstracts, 155 references were excluded and 69 full-text papers were analyzed. In the final analysis, 34 references were included, including 46 cases. A flowchart illustrating the search strategy is shown in Figure 5. Studies included were either a case report or a case series.

Brazil, Peru, Argentina, Colombia, and England included all cases (65.2%, 26%, 4.3%, 2.1%, and 2.1%, respectively). The baseline features are described in Table 1. A total of 46 patients were included, 32 (71.1%) males, mean age 35.2 years (range 5 to 68 years old). All patients were diagnosed with paracoccidioidomycosis (*Paracoccidioides* spp.). Inflammatory bowel disease was present in one case, with ulcerative colitis.

The most common clinical presentation was abdominal pain and weight loss, present in 31 (67.3%) cases, followed by diarrhea and cervical, axillary, inguinal, or other sites of lymphadenopathy (65.2% and 36.9%, respectively). Cutaneous manifestation and fever were present in 16 (34.7%) patients and lower gastrointestinal bleeding was present in 14 cases (30.4%). Only 7 (15.2%) patients presented with oral ulcers. In 10 (21.7%) cases, the disease presentation mimicked CD. The most common gastrointestinal locations were the large intestine, small intestine, and mouth (78.2%, 52.1%, 19.5%, respectively). In the intestine, the most specific locations were ileum, cecum, ascending, and transverse colon (20.5%, 19.1%, and 10.9%, respectively). Colonoscopy was performed in 28 (60.8%) patients and 45 (97.8%) underwent biopsy. The main characteristics of these and other tests are described in Table 2.

Medications used were described in 42 (91.3%) cases reported. Among these, 19 (41.3%) patients used itraconazole; 17 (36.9%) patients used amphotericin B; 12 (26%) underwent surgical intervention; 12 (26%) used sulfamethoxazole-trimethoprim and 6 (13%) used sulphadiazine. Considering only patients with available data, outcome was favorable for 34 (87.1%) patients; only 5 (12.8%) patients died. The mean time for signs and symptoms to disappear was 271 days, ranging from 18 to 2,555 days.

Discussion

This was a systematic review of clinical presentations and outcomes of patients with PCM infection involving the gastrointestinal tract, mimicking inflammatory bowel disease in some cases.

PCM is an endemic mycotic disease found in Central and South America, typically causing asymptomatic pulmonary infection.⁴⁴ The presented review found that most reported cases originated from South America, with a higher prevalence in Brazil (65.2%). The only reported case originating outside Central or South America was reported in England,²³ but the patient had been to Costa Rica one year before symptoms from the infection began.

Patients with PCM infection are usually male, with a male/female ratio of 13:1 in Brazil,² age average between 30 and 50 years old,⁴⁴ and rarely occurring in children and teenagers.⁴⁵ This infection predominates in males due to the protection provided by estrogen, which hinders the transformation of conidia and mycelial fragments into yeast cells, the pathogenic form of the fungus.^{6,46} Our analysis was compatible with the available epidemiological data, demonstrating a mean age of 35.2 years old and a higher prevalence in men (71.1%). Rural workers were the most frequently affected by PCM.^{1,2,6}

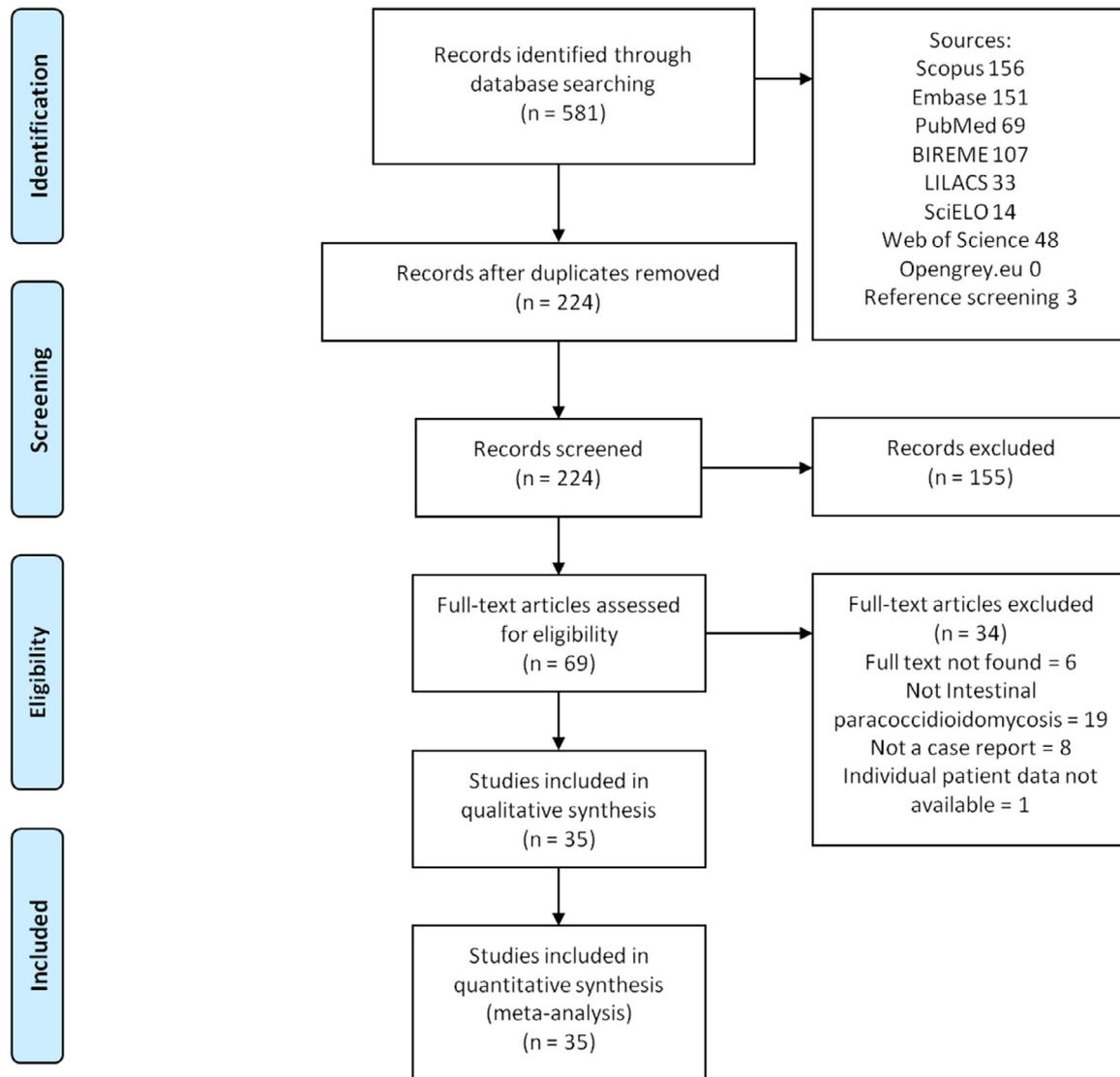


Figure 5 – Prisma Flowchart for the systematic review.

The fungus is inhaled,⁴⁵ which makes the lungs and the upper airways the first affected sites.⁴⁷ The infection can evolve to two classic presentations: acute or subacute juvenile form, with important involvement of reticuloendothelial system, including spleen, liver, lymph nodes, and bone marrow dysfunction,^{2,45} or chronic adult form (90% of cases), with significant lung involvement and sometimes extrapulmonary lesions,⁴⁷ including oral mucosa, skin, central nervous system, bowels, bone, adrenal, and genital organs. This represents endogenous reactivation years after initial contact.⁴⁵ The fungus can disseminate to any part of the body by hematogenous or lymphatic route.^{15,47} Also, gastrointestinal involvement can happen due to ingestion of *Paracoccidioides* spp.¹⁵ In these cases, abdominal pain and diarrhea are the most common symptoms, also present in our patient. However, other manifestations were reported, such as hematochezia, mucus in stools, hepatomegaly, vomiting, and, less commonly, regurgitation, intestinal motility alterations, hiccups, and palpable abdominal mass.³⁸

The gastrointestinal PCM can affect any part of the digestive system. In the presented review, the most common location of the disease was the colon, followed by the small intestine and mouth. Most intestinal alterations are found in the segments rich in lymphoid tissues, such as ileum, cecum, appendix, and the ascending colon.^{15,47} This information is compatible with our reported case, which demonstrated the presence of severe inflammation in the patient's ileum, large intestine, and pericolic lymph nodes, which first mimicked acute appendicitis. Afterwards, it presented with colonic ulcers which evolved into strictures, mimicking stricturing CD. Lesions in the esophagus, stomach, and anus are less common than in other sites.⁴⁵

The most common symptoms found were abdominal pain (67.3%), weight loss (67.3%), and diarrhea (65.2%). This is also commonly found in patients diagnosed with inflammatory bowel disease.⁴⁸ Intestinal PCM has been previously described as a condition that can mimic other diseases, especially CD,⁶ since this chronic auto-inflammatory condition can affect

Table 1 – Baseline features in 46 patients with gastrointestinal paracoccidioidomycosis.

Variable	Patients n = 46 (100%)
Mean age (yr) ± SD	35.2 ± 16.8
Sex (male)	32 (71.1)
Symptoms	
Abdominal pain	31 (67.3)
Weight Loss	31 (67.3)
Diarrhea	30 (65.2)
Lymphadenopathy	
Cervical	16 (34.7)
Axillar	5 (10.8)
Inguinal	5 (10.8)
Others	3 (6.5)
Cutaneous Manifestation	16 (34.7)
Fever	16 (34.7)
Hematochezia	14 (30.4)
Stools	10 (21.7)
Mucus	9 (19.5)
Pus	1 (2.1)
Pale Skin	11 (23.9)
Hepatomegaly	10 (21.7)
Vomiting	10 (21.7)
Abdominal Mass	8 (17.3)
Oral ulcers	7 (15.2)
Abdominal Distension	5 (10.8)
Anorexia	4 (8.7)
Jaundice	4 (8.7)
Constipation	3 (6.5)
Fatigue	3 (6.5)
Melena	1 (2.1)
Mean of laboratory tests ± SD	
Hb (g/dL)	8.8 ± 3.2
Ht (%)	28.2 ± 6.5
ESR (mm/hour)	52.6 ± 22
WBC (cells/ μ L)	11940 ± 10822
Albumin (g/dL)	2.08 ± 0.8
Gastrointestinal Involvement	
Large Intestine	36 (78.2)
Small Intestine	24 (52.1)
Mouth	9 (19.5)
Anus	2 (4.3)
Esophagus	1 (2.1)
Inflammatory bowel disease	
Ulcerative Colitis	1 (2.1)
Crohn-Like Behavior	10 (21.7)
Biopsy	45 (97.8)
Treatment	
Itraconazole	19 (41.3)
Amphotericin B	17 (36.9)
Surgical intervention	12 (26)
Sulfamethoxazole-trimethoprim	12 (26)
Sulphadiazine	6 (13)
Others	13 (28.2)
Outcome	
Recovery	34 (87.1)
Death	5 (12.8)
Symptoms improvement(mean days) ± SD	271 ± 215

any part of the digestive tract.⁴⁸ Therefore, intestinal PCM should be considered as a differential diagnosis for inflammatory bowel disease in endemic areas. In the presented systematic review, 10 patients developed a clinical syndrome that mimicked CD, presenting colonoscopies with multiple

superficial or deep colon ulcers intercalated by areas with normal mucosa.^{13,14,18,35,36} This information highlights the importance of endoscopic tests and biopsies for adequate diagnosis of intestinal ulcers.

PCM infection may be opportunistic in patients with reduced cellular immunity either caused by another disease or by immunosuppressant treatment.⁴⁹ The most commonly found correlations are cancer, HIV infection, and the use of immunosuppressive drugs.^{6,34} Concomitant IBD was observed in two patients diagnosed with PCM infection in the current review: a man with Ulcerative Colitis²³ and a woman with Chron's disease.⁵⁰ The patient was on immunosuppressive medications to treat the disease. According to the reported cases, the impaired immunity caused by the immunosuppressive therapy might have increased the risk for fungal infection.

Regarding laboratory data, anemia was the most common finding, with a mean hemoglobin of 8.8 g/dL and a mean hematocrit of 28.2%. Anemia is a common finding in patients with the acute/subacute form of PCM infection, generally associated with bone marrow involvement.⁴ Mucosal involvement resulting in gastrointestinal bleeding in the forms of hematochezia (30.4%) and melena (2.1%), can also contribute to the development of anemia.

The best tool for diagnosis of PCM infection is the identification of fungal elements suggestive of the infection in fresh examination of sputum, lesion scraps, lymph node, or biopsy of the affected organ.^{2,49} Typical histology shows inflammation signs and granulomas rich in epithelioid and giant cells containing variable amounts of fungal forms.¹⁵ Anatomopathological study of the biopsies of the reported case described fungal structures shaped as a ship's pilot wheel in Grocott-Gomori's staining, usually found in this disease. In the current review, 97.8% of the patients underwent biopsy of the affected organ to confirm the diagnosis.

Paracoccidioides spp. are sensitive to most systemic antifungals. A Brazilian guideline⁴⁹ published in 2017 is the current consensus for the clinical management of this disease. The guideline suggests the use of itraconazole 200 mg daily for 9 to 18 months in mild and moderate cases of PCM.⁴⁹ For patients with severe and systemic forms of PCM, the use of amphotericin B in deoxycholate or lipid formulation is suggested for the time necessary for the patient's clinical stability and transition to oral medication.⁴⁹ The antifungal therapy to the reported case was chosen based on this guideline. Furthermore, surgical intervention and antifungal therapy can be associated to achieve better results. Our review demonstrated that the cure rate of the infection was 87.1% and the most common treatment option was itraconazole (41.3%) followed by amphotericin B (36.9%). Sulfamethoxazole-trimethoprim and sulfadiazine are no longer used. The treatment goal is to reduce the fungal load and allow cellular immunity to recover, so the patient can live without disease relapses, achieving balance between parasite and host.⁴⁹

After the establishment of the best treatment option, patients diagnosed with PCM infection must keep an outpatient follow-up in order to reach the cure criteria, which is based on clinical, mycological, radiological and immunological parameters.^{46,49} Clinical cure is achieved when the

Table 2 – Summary of systematically reviewed clinical cases of gastrointestinal paracoccidioidomycosis.

Reference	Country	Age	Sex	Clinical presentation	GI involvement	IBD	Crohn-like behavior	Treatment	Outcome	Quality assessment
Vieira ¹¹ , 2001	Brazil	60	M	Weight loss, coughing, dyspnea, dysphonia, ulcerated anal lesion, sphincter hypony	Large intestine, rectum	No	No	SFD	Recovery	High
Muñoz Urribarri ¹² , 2006	Peru	5	M	Vomiting, abdominal pain, fever	Large intestine	No	No	ICZ, SI	Recovery	High
Duani ¹³ , 2012	Brazil	24	M	Fatigue, weight loss, diarrhea, hematochezia, abdominal pain, fever	Large intestine	No	Yes	SMZ-TMP, AmB, ICZ, SFD	Recovery	High
Penna ¹⁴ , 1979	Brazil	8	F	Anorexia, diarrhea, hematochezia, abdominal pain, fever	Large intestine, rectum	No	Yes	SMZ-TMP	Recovery	High
Bravo ¹⁵ , 2010	Peru	39	F	Weight loss, diarrhea, hematochezia, abdominal pain, fever	Large intestine	No	No	AmB	Death	Moderate
Benard ¹⁶ , 2013	Brazil	58	F	Weight loss, diarrhea, fever	Large intestine	No	No	ICZ	Recovery	High
Benard ¹⁶ , 2013	Brazil	56	F	Two colonic polyps found on routine colonoscopy	Large intestine	No	No	ICZ, endoscopic removal of the polyps	Recovery	Moderate
Alcántara ¹⁷ , 2017	Peru	29	F	Weight loss, diarrhea, hematochezia, abdominal pain, fever, dizziness	Large intestine, rectum	No	No	AmB, ICZ	Recovery	Moderate
Alcántara ¹⁷ , 2017	Peru	24	M	Fatigue, weight loss, diarrhea, dizziness, dyspnea	Small and large intestine	No	No	AmB, ICZ	Recovery	Moderate
Alcántara ¹⁷ , 2017	Peru	29	M	Weight loss, diarrhea, abdominal pain, severe anemia	Large intestine	No	No	ICZ, SMZ-TMP	Recovery	Moderate
Martinez ¹⁸ , 2006	Brazil	22	M	Weight loss, diarrhea, abdominal pain, fever	Small and large intestine	No	Yes	ICZ	Recovery	Moderate
Verona ¹⁹ , 1998	Peru	36	M	Weight loss, abdominal pain, anal fissure, abdominal mass	Small and large intestine	No	No	ICZ	Recovery	Moderate
Bravo ²⁰ , 2011	Peru	34	M	Upper palate, nose, mouth and right foot ulcers, weight loss, diarrhea, hematochezia	Large intestine	No	No	AmB, ICZ	Recovery	Moderate
Hahn ²¹ , 2003	Brazil	22	M	Weight loss, vomiting, abdominal pain, hepatomegaly, intestinal obstruction	Small intestine	No	No	SMZ-TMP, KCZ, AmB, FCZ, ICZ, SI	Recovery	High
Meyer ²² , 1982	Brazil	9	F	Diarrhea, vomiting, abdominal pain, abdominal mass	Small and large intestine	No	No	SFD, SMZ-TMP, SI	Recovery	Low
Healy ²³ , 2020	England	52	M	Diarrhea, hematochezia, fever	Large intestine	UC	No	ICZ, SI, Posaconazol, Voriconazole, Azathioprine	Recovery	Low
Galeazzi ²⁴ , 2011	Brazil	68	F	Weight loss, diarrhea, abdominal mass	Small and large intestine	No	Yes	ICZ, SFD, AmB	NR	Moderate
Vinagre ²⁵ , 2004	Brazil	22	M	Weight loss, diarrhea, hematochezia, abdominal pain, fever	Large intestine	No	No	NR	NR	High
Freitas Junior ²⁶ , 1991	Brazil	36	M	Anorexia, vomiting, abdominal pain, fever	Small intestine	No	No	SI	Recovery	Moderate
Gava ²⁷ , 2015	Brazil	20	M	Weight loss, hematochezia	Mouth, small and large intestine, rectum	No	Yes	AmB	Recovery	High
Ribas ²⁸ , 2008	Brazil	27	M	Weight loss, diarrhea, hematochezia, vomiting, abdominal pain	Large intestine	No	No	SMZ-TMP, FCZ	Recovery	Moderate
Rocha ²⁹ , 1997	Brazil	26	M	Diarrhea, abdominal pain, ascites	Small and large intestine, rectum	No	No	KCZ, SI, Sulfisoxazole	Recovery	High
Rocha ²⁹ , 1997	Brazil	30	M	Anorexia, weight loss, diarrhea, abdominal pain	Large intestine	No	No	Antifungal therapy	Death	Moderate
Lomazi ⁸ , 2018	Brazil	13	M		Large intestine, rectum	No	Yes	ICZ, AmB	Recovery	Moderate

Table 2 (continued)

Reference	Country	Age	Sex	Clinical presentation	GI involvement	IBD	Crohn-like behavior	Treatment	Outcome	Quality assessment
Chojniak ³⁰ , 2000	Brazil	57	NR	Weight loss, diarrhea, hematochezia, abdominal pain	Small and large intestine	No	No	KCZ, SI	Recovery	Moderate
Hossne ³¹ , 2005	Brazil	48	M	Weight loss, abdominal pain	Small and large intestine	No	Yes	SI	Recovery	Moderate
Gorodner ³² , 2004	Argentina	59	M	Weight loss, abdominal pain	Mouth, small intestine	No	No	SI	NR	Moderate
Rüssel ³³ , 2016	Argentina	63	M	Intestinal infarction, ischemia of the right lower limb	Small and large intestine	No	No	ICZ, SI	Death	Moderate
Golçalves ³⁴ , 1996	Brazil	12	F	Weight loss, diarrhea, hematochezia, vomiting, abdominal pain, fever, hepatomegaly, splenomegaly	Small and large intestine, rectum	No	No	SMZ-TMP, AmB	Recovery	High
Cury ³⁵ , 2000	Brazil	43	M	Weight loss, vomiting, abdominal pain	Small and large intestine	No	Yes	SMZ-TMP	Recovery	Moderate
Rodríguez ³⁶ , 2018	Colombia	26	M	Weight loss, diarrhea, abdominal pain	Small and large intestine	No	Yes	SMZ-TMP, AmB, SI	Recovery	Moderate
Troncon ³⁷ , 1981	Brazil	23	M	Vomiting, abdominal pain, fever, hepatomegaly, jaundice; ascites	NR	No	No	AmB, SFD	Recovery	High
Troncon ³⁷ , 1981	Brazil	26	M	Diarrhea, hepatomegaly, jaundice; ascites	NR	No	No	SFD	NR	High
Berni ³⁸ , 2010	Brazil	53	M	Weight loss, diarrhea, abdominal pain, fever, hepatomegaly	Mouth, large intestine	No	No	SMZ-TMP, AmB; ICZ; Pyrazinamide	Recovery	High
Berni ³⁸ , 2010	Brazil	36	F	Weight loss, abdominal pain, fever, hepatomegaly, jaundice; ascites	Mouth, large intestine	No	No	SMZ-TMP, AmB	Recovery	Moderate
Berni ³⁸ , 2010	Brazil	50	M	Weight loss, abdominal pain, fever, hepatomegaly, jaundice, oral lesions	Mouth, small intestine	No	No	SMZ-TMP, AmB	Recovery	High
Avritchir ³⁹ , 1978	Brazil	23	NR	Diarrhea, palpable abdominal mass	Small intestine	No	No	AmB	Recovery	Moderate
Avritchir ³⁹ , 1978	Brazil	20	NR	Diarrhea, abdominal pain, palpable abdominal mass	Small intestine	No	No	Antifungal therapy	Recovery	Moderate
Avritchir ³⁹ , 1978	Brazil	36	M	Diarrhea, hematochezia, abdominal pain, oral ulcers	Mouth, small intestine	No	No	NR	NR	Low
Fernández ⁴⁰ , 1979	Peru	23	M	Diarrhea, hematochezia, abdominal pain	Small and large intestine	No	Yes	NR	NR	Low
Fernández ⁴⁰ , 1979	Peru	63	M	Increased frequency of bowel movements	Large intestine	No	No	NR	NR	Moderate
Neves-Silva ⁴¹ , 2018	Brazil	36	M	Weight loss, diarrhea, vomiting, oral ulcers, dysphagia	Mouth, small and large intestine, rectum	No	No	ICZ, SI	Recovery	High
Martinez ⁴² , 1984	Brazil	35	F	Anorexia, fatigue, weight loss, diarrhea, hematochezia, vomiting, abdominal pain, fever, hepatomegaly, jaundice	Esophagus, small and large intestine	No	No	NR	Death	High
León ⁴³ , 2010	Peru	66	M	Weight loss, dyspnea; dry cough, oral lesions	Mouth	No	No	ICZ	Recovery	Moderate
León ⁴³ , 2010	Peru	34	M	Weight loss, diarrhea, oral ulcers, odynophagia, dry cough	Mouth, small and large intestine	No	No	ICZ, AmB	Recovery	Moderate
León ⁴³ , 2010	Peru	40	F	Weight loss, diarrhea, hepatomegaly	Large intestine	No	No	AmB	Death	Moderate

AmB, Amphotericin B; F, Female; FCZ, Fluconazole; GI, gastrointestinal; IBD, Inflammatory bowel disease; ICZ, Itraconazole; KCZ, Ketoconazole; M, Male; MSZ, Mesalazine; NR, not reported; SFD, Sulfadiazine; SI, Surgical Intervention; SMZ-TMP, sulfamethoxazole-trimethoprim; UC, ulcerative colitis.

signs and symptoms of the disease are no longer present,⁴⁶ which includes wound healing, regression of adenomegaly and stabilization of body weight.⁴⁹ Micological cure represents negative results on mycological tests after efficacious treatment.^{46,49} Radiological criteria is based on the image investigation of the lungs, the most commonly affected organ by PCM.^{46,49} Immunological cure consists on the decrease of serum fungus antibodies, which become undetectable or at very low concentration.^{46,49} The term definitive cure must not be used, based on the impossibility of eradicating the fungus from the organism completely.⁴⁹

According to our findings, surgical intervention was necessary in 15% of the cases. In these cases, surgery was not considered as a treatment for the PCM, but was used as therapy for PCM complications, such as intestinal obstruction²¹ or structuring disease,^{26,31} acute abdomen,^{26,32,41} exploratory laparotomy for diagnostic purposes,^{26,41} and management of complications due to a major comorbidity.³³ In our reported case, the patient underwent two surgeries. The first was due to a suspicion of acute appendicitis and the second was an emergency total colectomy due to bowel obstruction.

In conclusion, PCM should be suspected in patients who live or recently visited endemic areas, such as Central or South America, specially as a differential diagnosis for inflammatory bowel disease. Symptoms mimicking inflammatory bowel disease, such as abdominal pain, weight loss, diarrhea, and blood in stools are also present in intestinal PCM. Histologic studies, such as biopsies or surgical resection areas, are necessary for adequate diagnosis. Antifungal drugs such as itraconazole for mild/moderate disease and amphotericin B for severe disease seem to be the first treatment option and achieve significant success rates. Nevertheless, the considerable mortality are to be pointed out, and these patients should be managed with celerity.

Conflicts of interest

The authors have no conflict of interest to disclose.

Author contributions

All authors contributed to study concept and design, and drafting of the manuscript; all authors contributed to acquisition of data, analysis, and interpretation of data; Ballotin VR contributed to statistical analysis; Soldera J contributed to study supervision; all authors contributed to critical revision of the manuscript for important intellectual content.

Appendix A Search Strategy

Scopus

TITLE-ABS-KEY (("Paracoccidioidomycosis" OR "Paracoccidioides" OR "paracoccidioidal" OR "Blastomycosis" OR

"Blastomyces")) AND (("colon" OR "intestinal" OR "bowel" OR "ileum" OR "colonic" OR "Colitis" OR "Inflammatory Bowel Disease" OR "Crohn"))

Web of Science

TOPIC: (("Paracoccidioidomycosis" OR "Paracoccidioides" OR "paracoccidioidal" OR "Blastomycosis" OR "Blastomyces")) AND TOPIC: (("colon" OR "intestinal" OR "bowel" OR "ileum" OR "colonic" OR "Colitis" OR "Inflammatory Bowel Disease" OR "Crohn"))

Embase

('paracoccidioidomycosis' OR 'paracoccidioides' OR 'paracoccidioidal' OR 'blastomycosis' OR 'blastomyces') AND ('colon' OR 'intestinal' OR 'bowel' OR 'ileum' OR 'colonic' OR 'colitis' OR 'inflammatory bowel disease' OR 'crohn')

PubMed

('Paracoccidioidomycosis' OR "Paracoccidioides" OR "paracoccidioidal" OR "Blastomycosis" OR "Blastomyces") AND ("colon" OR "intestinal" OR "bowel" OR "ileum" OR "colonic" OR "Colitis" OR "Inflammatory Bowel Disease" OR "Crohn")

SciELO

(*("Paracoccidioidomycosis" OR "Paracoccidioides" OR "paracoccidioidal" OR "Blastomycosis" OR "Blastomyces") AND ("colon" OR "intestinal" OR "bowel" OR "ileum" OR "colonic" OR "Colitis" OR "Inflammatory Bowel Disease" OR "Crohn"))

BIREME

((("Paracoccidioidomycosis" OR "Paracoccidioides" OR "paracoccidioidal" OR "Blastomycosis" OR "Blastomyces")) AND (("colon" OR "intestinal" OR "bowel" OR "ileum" OR "colonic" OR "Colitis" OR "Inflammatory Bowel Disease" OR "Crohn")))

LILACS

("Paracoccidioidomycosis" OR "Paracoccidioides" OR "paracoccidioidal" OR "Blastomycosis" OR "Blastomyces") [Palavras] and ("colon" OR "intestinal" OR "bowel" OR "ileum" OR "colonic" OR "Colitis" OR "Inflammatory Bowel Disease" OR "Crohn") [Palavras]

Opengrey.eu

("Paracoccidioidomycosis" OR "Paracoccidioides" OR "paracoccidioidal" OR "Blastomycosis" OR "Blastomyces") AND ("colon" OR "intestinal" OR "bowel" OR "ileum" OR "colonic" OR "Colitis" OR "Inflammatory Bowel Disease" OR "Crohn")

Appendix B

Table 3

Table 3 – Quality assessment of included cases of gastrointestinal paracoccidioidomycosis.

Reference	Case number	Selection	Ascertainment			Causality				Reporting	Quality assessment
		Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	Q 7	Q 8		
Vieira ¹¹ , 2001		No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Muñoz Urribarri ¹² , 2006		Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	High
Duani ¹³ , 2012		No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Penna ¹⁴ , 1979		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Bravo ¹⁵ , 2010		No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Moderate
Benard ¹⁶ , 2013	1	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Moderate
Benard ¹⁶ , 2013	2	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Moderate
Alcántara ¹⁷ , 2017	1	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	High
Alcántara ¹⁷ , 2017	2	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Moderate
Alcántara ¹⁷ , 2017	3	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Moderate
Martinez ¹⁸ , 2006		No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Verona ¹⁹ , 1998		No	Yes	No	Yes	No	Yes	No	Yes	Yes	Moderate
Bravo ²⁰ , 2011		Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Moderate
Hahn ²¹ , 2003		Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Moderate
Meyer ²² , 1982		No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Moderate
Healy ²³ , 2020		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Galeazzi ²⁴ , 2011		No	Yes	No	Yes	No	Yes	No	No	No	Low
Vinagre ²⁵ , 2004		No	Yes	No	No	No	Yes	No	No	No	Low
Freitas Junior ²⁶ , 1991		No	Yes	No	Yes	No	Yes	No	Yes	Yes	Moderate
Gava ²⁷ , 2015		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Ribas ²⁸ , 2008		No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Moderate
Rocha ²⁹ , 1997	1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Rocha ²⁹ , 1997	2	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Moderate
Lomazi ⁸ , 2018		No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Moderate
Chojniak ³⁰ , 2000		Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	Moderate
Hossne ³¹ , 2005		No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Moderate
Gorodner ³² , 2004		No	Yes	No	Yes	No	Yes	Yes	No	No	Moderate
Rüssel ³³ , 2016		No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Moderate
Golçalves ³⁴ , 1996		No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Cury ³⁵ , 2000		No	Yes	No	Yes	Yes	Yes	No	No	No	Moderate
Rodríguez ³⁶ , 2018		No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Troncon ³⁷ , 1981	1	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	High
Troncon ³⁷ , 1981	2	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	High
Berni ³⁸ , 2010	1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Berni ³⁸ , 2010	2	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Moderate
Berni ³⁸ , 2010	3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Avritchir ³⁹ , 1978	1	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Moderate
Avritchir ³⁹ , 1978	2	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Moderate
Avritchir ³⁹ , 1978	3	Yes	Yes	No	No	No	No	No	No	No	Low
Fernández ⁴⁰ , 1979	1	No	Yes	No	Yes	No	Yes	No	No	No	Low
Fernández ⁴⁰ , 1979	2	No	Yes	No	Yes	No	Yes	Yes	Yes	No	Moderate
Neves-Silva ⁴¹ , 2018		Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	High
Martinez ⁴² , 1984		Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	High
León ⁴³ , 2010	1	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	Moderate
León ⁴³ , 2010	2	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	Moderate
León ⁴³ , 2010	3	Yes	Yes	Yes	No	No	No	Yes	No	No	Moderate

Q 1: Did the patient(s) represent the whole case(s) of the medical centre? Q 2: Was the exposure adequately ascertained? Q 3: Was the outcome adequately ascertained? Q 4: Were other alternative causes that may explain the observation ruled out? Q 5: Was there a response to the specific treatment for paracoccidioidomycosis? Q 6: Was there a histological confirmation of the diagnosis? Q 7: Was follow-up long enough for outcomes to occur? Q 8: Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?

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