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CLINICAL CASE

Paracoccidioidomycosis with digestive manifestations in a pediatric patient

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Abstract

Background: *Paracoccidioidomycosis is a systemic infection caused by the fungus Paracoccidioides. It may present in two forms: an acute/subacute form, whose most frequent manifestations include weight loss, fever, anemia, and adenopathy, and a chronic condition with mainly respiratory symptoms. Digestive symptoms, although they may occur, are not frequently reported. Paracoccidioidomycosis usually affects adult male agricultural workers; thus, its presentation in children is rare.* **Case report:** *We describe the case of a 9-year-old male patient diagnosed with paracoccidioidomycosis, who showed abdominal pain and diarrhea as initial manifestations of the disease.* **Conclusions:** *This case is reported not only because of the age of presentation but also due to the existence of digestive symptoms from the onset of the disease, both infrequently reported in the literature.*

Keywords: *Paracoccidioidomycosis. Child. Diarrhea. Abdominal pain.*

Paracoccidioidomicosis con manifestaciones digestivas en un paciente pediátrico

Resumen

Introducción: *La paracoccidioidomicosis es una infección sistémica producida por el hongo Paracoccidioides. Se puede presentar de dos formas: una forma aguda/subaguda, cuyas manifestaciones más frecuentes incluyen pérdida de peso, fiebre, anemia y adenopatías, y una forma crónica con manifestaciones principalmente respiratorias. Las manifestaciones digestivas, aunque pueden presentarse, no se reportan frecuentemente. La paracoccidioidomicosis afecta usualmente a varones adultos que trabajan en labores agrícolas, por lo que su presentación en niños es poco frecuente.* **Caso clínico:** *Se describe el caso de un paciente de sexo masculino de 9 años de edad con diagnóstico de paracoccidioidomicosis, con dolor abdominal y diarrea como manifestaciones iniciales de la enfermedad.* **Conclusiones:** *Se reporta este caso, no solamente por la edad de presentación, sino también por la existencia de síntomas digestivos desde el inicio de la enfermedad, ambos reportados en forma infrecuente en la literatura.*

Palabras clave: *Paracoccidioidomicosis. Niño. Diarrea. Dolor abdominal.*

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Introduction

Paracoccidioidomycosis is a systemic fungal disease[1] with a restricted geographic distribution in Mexico and Central and South America. The most significant number of patients is registered in Brazil, with 80% of all reported cases, followed by Colombia, Venezuela, and Argentina[2]. It occurs most frequently in adult male agricultural workers due to exposure to the fungal habitat (soil), mainly in those who cultivate coffee, cotton, and tobacco[3].

Two clinical forms of the disease have been described: an acute/subacute form (juvenile type) and a chronic form (adult type). The former occurs in a smaller percentage of cases and includes weight loss, fever, anemia, and lymphadenopathy as clinical manifestations. In addition, liver, splenic, bone marrow, and gastrointestinal involvement may also be present[4], although the latter has not been frequently reported in the literature.

Here, we present the case of a 9-year-old male patient with paracoccidioidomycosis admitted to a hospital in northern Peru with digestive manifestations from the onset of infection.

Clinical case

We describe the case of a 9-year-old male patient from Tabaconas, a coffee-growing district in the Cajamarca region of Peru. He presented with a 10-week course of illness, which started with hyporexia and sporadic abdominal pain. After one week, liquid evacuations were present, mainly at night in the beginning, although later increased in frequency and volume until reaching 4 to 6 episodes per day. After six weeks, the abdominal pain intensified, with the addition of nausea, vomiting, and an unquantified sensation of thermal elevation. The frequency of bowel movements also increased to 8 to 10 episodes per day, for which he was admitted to a local general hospital. Given the poor clinical evolution and significant weight loss, the patient was referred to our hospital (Figure 1).

On admission, the patient was found afebrile, with cachexic facies, marked pallor, polyadenopathy, edema of the lower limbs, and diffuse abdominal pain on deep palpation. Initial laboratory tests showed moderate anemia, leukocytosis with neutrophilia and anisocytosis with mild hypochromia, prolonged prothrombin and activated partial thromboplastin time, increased C-reactive protein, severe hypoalbuminemia, moderate hyponatremia and hypokalemia (Table 1), as well as fecal leukocytes > 100 per field.

Sepsis of abdominal origin was diagnosed, and after cultures were taken, intravenous treatment with ceftriaxone (100 mg/kg/day) and metronidazole (30 mg/kg/day) was started. In addition, vitamin K (10 mg) was administered, and a blood transfusion and fresh frozen plasma were indicated. The differential diagnosis included metaxenic disease (bartonellosis, malaria), intestinal parasitosis, fungal colitis, tuberculosis, and lymphoma.

Other laboratory studies were requested, such as beta-2 microglobulin (normal results), IgM-IgG for toxoplasma, cytomegalovirus and herpes simplex, antibodies for SARS-CoV-2 virus, ELISA (enzyme-linked immunosorbent assay) for HIV (human immunodeficiency virus), smear for *Bartonella*, thick drop for malaria, test for bacillus Koch (BK) in gastric contents, stool, and urine; expanded serial parasitology, blood culture, urine culture, and stool culture, all negative.

A contrasted abdominal CT scan showed hepatomegaly and multiple mesenteric, para-aortic, and retroperitoneal lymphadenopathies (Figure 2). Due to suspecting a lymphoproliferative picture, a cervical lymph node biopsy was performed on hospital day 3 (HD3).

During the evolution of the disease, the patient presented abdominal pain of moderate intensity during feeding, persistent edema in the lower limbs, and a fecal flow between 2.5 and 4.5 g/kg/h, requiring replacement of losses with polyelectrolyte solution. On HD9, there was a slight improvement in the coagulation profile, with persistent hyponatremia, increased C-reactive protein, and decreased serum albumin values (Table 1), so it was decided to administer human albumin at a dose of 0.5 g/kg/day for three consecutive days.

The anatomopathological report was received with the following result: chronic granulomatous inflammatory process and multiple mycotic structures corresponding to *Paracoccidioides* (Figure 3). Intravenous treatment with amphotericin B was started at an initial test dose of 0.25 mg/kg/day, with good tolerance, gradually increasing at a rate of 0.25 mg/kg/day up to the therapeutic dose of 1 mg/kg/day.

The patient showed clinical improvement during the first week of treatment (HD14) with a fecal flow between 1.6 and 3.6 g/kg/h, a mild decrease in abdominal pain, and improvement in food acceptance. Although there was a decrease in peripheral blood neutrophils and C-reactive protein, severe hypokalemia was identified,

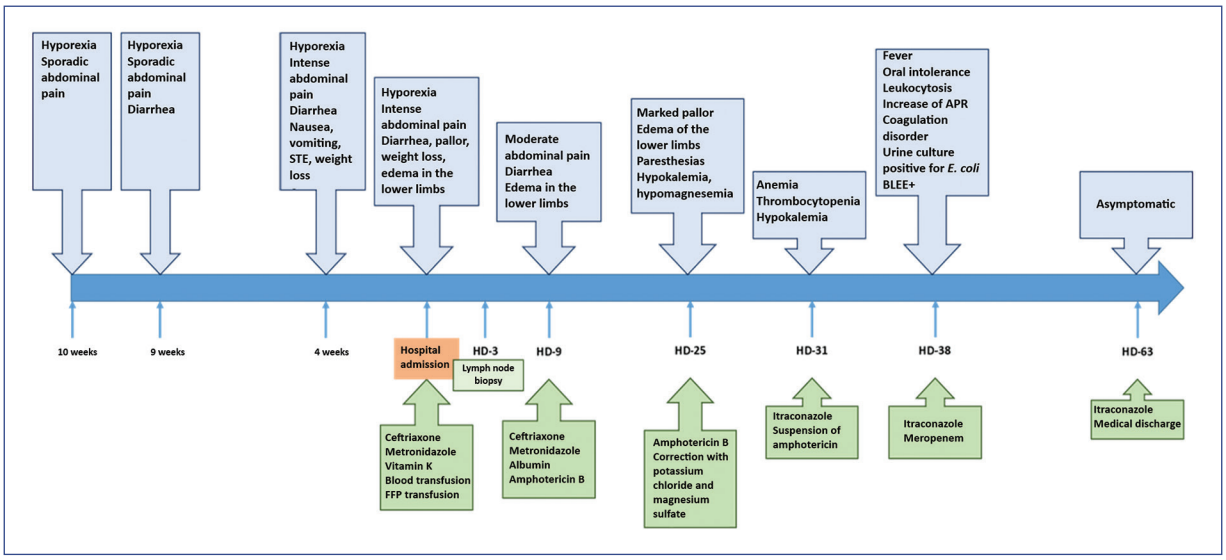

Figure 1. Clinical evolution of the patient. APR: acute phase reactants; FFP: fresh frozen plasma; HD: hospital day; STE: sensation of thermal elevation.

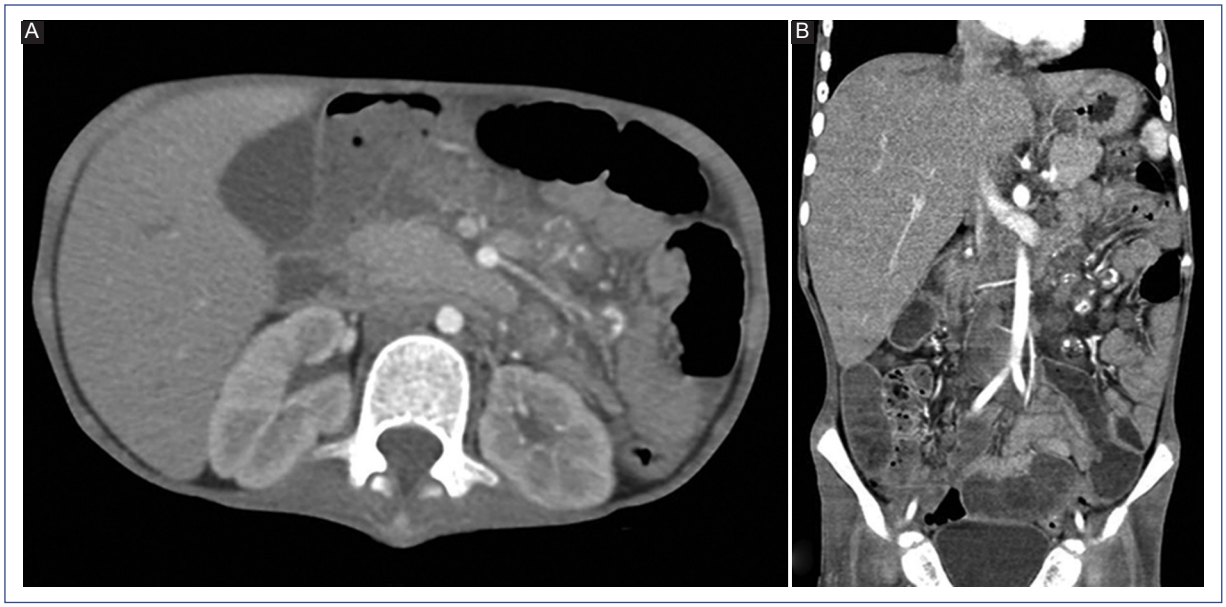

Figure 2. Contrast-enhanced abdominal CT scan. **A:** multiple ovoid mesenteric adenopathies. **B:** hepatomegaly, multiple retroperitoneal adenopathies with a tendency to conglomerate and some with internal calcification images.

requiring intravenous potassium correction and increased oral intake.

At the end of 12 days of treatment with amphotericin B (HD25), increased skin and mucosal pallor, and edema and paresthesia in the lower limbs were reported. Laboratory tests revealed severe anemia, hypokalemia, and hypomagnesemia, requiring blood transfusion and intravenous correction with potassium chloride and magnesium sulfate. Fecal output was registered at 1 g/kg/h.

Considering the favorable clinical evolution and the evidence of adverse effects (anemia, mild thrombocytopenia, and persistent hypokalemia with the need for frequent corrections with potassium chloride), it was

Table 1. Laboratory studies at admission and by hospital days

	Admission	HD 9	HD 14	HD 25	HD 29	HD 38	HD 51	HD 63
Hemoglobin (g/dL)	7.9	10.2	8.7	6.1	8.9	9.1	8	8.5
Leukocytes (x10^3/mm^3)	20.2	17.64	13.06	14.57	11.79	14.9	8.5	10.1
Rods (x10^3/mm^3)	0	0	0.13	0	0	0.59	0	0.1
Neutrophils (x10^3/mm^3)	18.18	14.11	11.69	10.49	8.3	11.9	3.6	5.35
Platelets (x10^3/mm^3)	353	208	250	197	108	53	556	-
INR	1.47	1.37	-	-	-	1.53	-	-
Activated partial thromboplastin time (s)	51	45.4	-	-	-	63.2	-	-
Glucose (mg/dL)	90	85	-	80	85	84	-	-
Urea (mg/dL)	8	-	-	21	-	9	11	37
Creatinine (mg/dL)	0.16	-	-	0.18	-	0.08	0.09	0.23
Aspartate aminotransferase (U/L)	13	11	11	21	-	14	17	22
Alanine aminotransferase (U/L)	11	6	8	15	-	14	13	20
Total protein (mg/dL)	5.46	4.5	4.07	5.35	4.89	5.47	6.61	7.47
Albumin (mg/dL)	1.85	1.31	2.09	2.32	2	2.48	2.59	3.25
C-reactive protein (mg/L)	29.2	47.3	44.6	18.4	22.3	54.1	4.9	4.5
Sodium (mmol/L)	127	127.9	136	145.8	138.8	130.1	136.1	138.2
Potassium (mmol/L)	2,97	3.81	2.42	2.52	2.29	3.43	4.86	4.67
Chloride (mmol/L)	106.7	107.9	104.9	116.2	116	106.7	109.9	104.9
Calcium (mmol/L)	1.2	1.3	1.32	1.09	1.1	1.07	1.25	1.26
Magnesium (mg/dL)	-	-	-	1	1.5	-	-	-

HD: hospital days; INR: international normalized ratio.

decided to discontinue amphotericin B on day 22 (HD31) of treatment with this drug, and to initiate itraconazole orally at a dose of 8 mg/kg/day with good tolerance.

On HD38, the patient presented with fever and oral intolerance, with a hemogram showing leukocytosis and increased neutrophils and rods, coagulation disorder, increased C-reactive protein, hyponatremia (Table 1), and a urine culture positive for *E. coli* ESBL (extended-spectrum beta-lactamase), for which meropenem was administered at a dose of 60 mg/kg/day, with good clinical response.

Finally, the patient was discharged on HD63 to continue treatment with itraconazole and medical checkups in the primary care unit.

For the present publication, informed consent was obtained from the patient's father and authorization from the ethics committee of the Hospital Regional Lambayeque.

Discussion

Paracoccidioidomycosis is a disease caused by fungi of the genus *Paracoccidioides*, including the *Paracoccidioides brasiliensis* and *Paracoccidioides lutzii* species, which are thermally dimorphic and are found as mycelia between 22-26°C and as yeast at 37°C[1]. Multilocus sequence typing (MLST) has identified at least five phylogenetic groups of *P. brasiliensis*: S1a, S1b, PS2, PS3, and PS4, which have a particular geographic distribution[5]. The phylogenetic species S1a and S1b predominate in southeastern and southern Brazil, Argentina, and Paraguay; PS2 has been reported less frequently, and human cases have only been reported in Venezuela and southeastern Brazil, while PS3 and

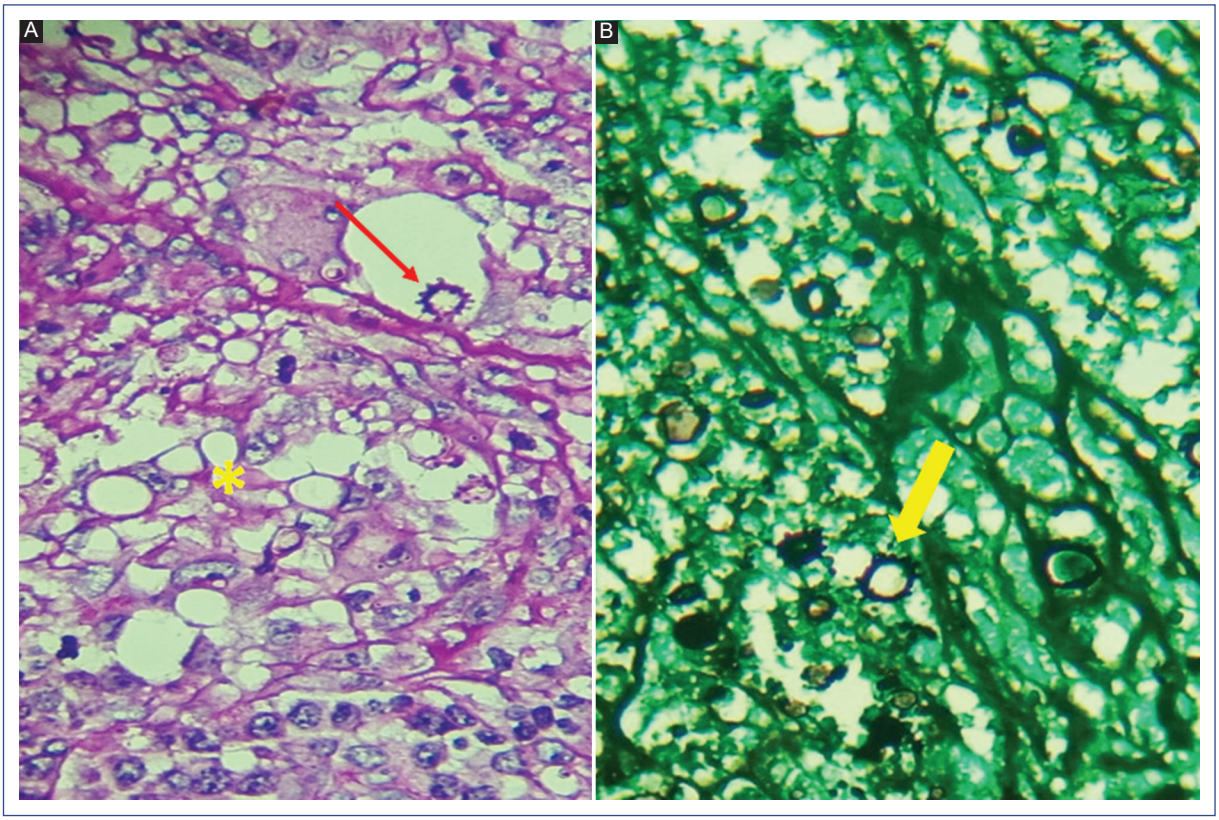

Figure 3. Lymph node biopsy. **A:** hematoxylin-eosin (HE) stain 400X. Chronic granulomatous inflammatory process (yellow asterisk) where round yeasts are observed (red arrow). **B:** special methenamine-silver stain 400X. Multiple multigemant yeasts in the shape of a ship's rudder corresponding to *Paracoccidiodes* are observed (yellow arrow).

PS4 are endemic exclusively in Colombia and Venezuela, respectively[4].

Prevalence in areas considered endemic can reach 50-70% of the adult population, with approximately 10 million people infected by this fungus[1]. Although paracoccidioidomycosis occurs as natural infection, mainly in humans, sporadic infections have been reported in domestic and wild animals, mainly in some species of armadillos[6].

In adults, the chronic form of the disease is more prevalent in males between 30 and 60 years of age, with an average male-to-female ratio of 13:1 in Brazil and up to 70:1 in other South American countries[7]. Male predominance may be due to the protective effect of beta-estradiol. This female hormone could inhibit the yeast phase of the fungus, explaining why this gender difference is not observed before puberty, during which the acute/subacute form of the disease usually occurs[4].

Paracoccidioides spp. enter by inhalation into the lungs, where activated neutrophils and macrophages can block fungal growth and dissemination in most individuals, forming granulomas at sites of primary infection and sometimes in metastatic foci that may contain viable but inactive fungal forms[8]. After a prolonged latency period (years), when the immune balance is lost due to some conditions that have not yet been fully identified, the infection can spread to any part of the body by hematogenous or lymphatic routes, generating a florid disease (chronic form of paracoccidioidomycosis)[4].

Less frequently, the systemic disease may also progress from the primary focus of infection without a latency period, accounting for less than 10% of cases. It presents a rapid clinical deterioration of the patient (acute-subacute or juvenile paracoccidioidomycosis), which may appear as early as 45 days after exposure[9]. In the latter case, dissemination of the infection to the reticuloendothelial system manifests with lymphadenopathy, hepatosplenomegaly, and anemia due to bone marrow dysfunction, frequently accompanied by fever and weight loss, with pulmonary involvement being very infrequent, unlike the chronic form, as occurred in the present case. Laboratory tests may show anemia (89%), eosinophilia (76%), hypoalbuminemia (73%),

hyperbilirubinemia (44%), and mild hypertransaminasemia (20%)[10]. In addition, our patient also presented with coagulation disorders, a situation not frequently reported in this infection[11] that could be associated with hepatic involvement.

Digestive involvement is uncommon in children and can also be caused by ingestion of *Paracoccidioides* spp[12]. Our patient showed abdominal pain and diarrhea in the early stages of the disease, which are the most frequent symptoms of gastrointestinal tract involvement. However, other manifestations have also been described, such as hematochezia, mucus in the stool, vomiting and, less frequently, regurgitation, altered intestinal motility, hiccups, and palpable abdominal mass[12-15]. A recent review reported that the most common location of the disease was the colon, followed by the small intestine and mouth, with the most significant involvement in segments of the gastrointestinal tract rich in lymphoid tissue such as the ileum, cecum, appendix, and ascending colon[14].

In severe disease with multisystem involvement, as in this patient, intravenous treatment with amphotericin B is recommended, followed by administration of itraconazole after observing an improvement in clinical status (between 20 and 40 days of intravenous therapy)[4] since amphotericin B can be associated with adverse effects such as hypokalemia and hypomagnesemia. Therefore, we administered amphotericin B for 22 days and observed several adverse effects, a situation that improved upon rotation to itraconazole.

In conclusion, we reported this case not only because of the age of presentation but also due to the digestive symptoms observed since the onset of the disease, which were the reason for consultation and have not been frequently reported in the literature within the clinical manifestations of paracoccidioidomycosis.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflict of interest.

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References

1. Martinez R. New trends in paracoccidioidomycosis epidemiology. J Fungi (Basel). 2017;3:1.
2. Martinez R. Epidemiology of paracoccidioidomycosis. Rev Inst Med Trop Sao Paulo. 2015;57(Suppl 19):11-20.
3. Calle D, Rosero DS, Orozco LC, Camargo D, Castañeda E, Restrepo A. Paracoccidioidomycosis in Colombia: an ecological study. Epidemiol Infect. 2001;126:309-15.
4. Shikanai-Yasuda MA, Mendes RP, Colombo AL, Queiroz-Telles F, Kono ASG, Paniago AMM, et al. Brazilian guidelines for the clinical management of paracoccidioidomycosis. Rev Soc Bras Med Trop. 2017;50:715-40.
5. Muñoz JF, Farrer RA, Desjardins CA, Gallo JE, Sykes S, Sakthikumar S, et al. Genome diversity, recombination, and virulence across the major lineages of *Paracoccidioides*. mSphere. 2016;1:e00213-16.
6. Silveira LH, Paes RC, Medeiros EV, Itano EN, Camargo ZP, Ono MA. Occurrence of antibodies to *Paracoccidioides brasiliensis* in dairy cattle from Mato Grosso do Sul, Brazil. Mycopathologia. 2008;165:367-71.
7. Blotta MH, Mamoni RL, Oliveira SJ, Nouér SA, Papaiordanou PM, Goveia A, et al. Endemic regions of paracoccidioidomycosis in Brazil: a clinical and epidemiologic study of 584 cases in the southeast region. Am J Trop Med Hyg. 1999;61:390-4.
8. de Castro LF, Ferreira MC, da Silva RM, Blotta MH, Longhi LN, Mamoni RL. Characterization of the immune response in human paracoccidioidomycosis. J Infect. 2013;67:470-85.
9. Buccheri R, Khoury Z, Barradas-Barata LC, Benard G. Incubation period and early natural history events of the acute form of paracoccidioidomycosis: lessons from patients with a single *Paracoccidioides* spp. exposure. Mycopathologia. 2016;181:435-9.
10. Pereira RM, Bucaretchi F, Barison EM, Hessel G, Tresoldi AT. Paracoccidioidomycosis in children: clinical presentation, follow-up and outcome. Rev Inst Med Trop Sao Paulo. 2004;46:127-31.
11. Choque-Barrera M, Suarez-Barrientos EL, Calderón-López ME. Paracoccidioidomicosis, a propósito de un caso. Gac Med Bol. 2015;38:30-3.
12. Bravo EA, Zegarra AJ, Piscoya A, Pinto JL, de Los Rios RE, Prochazka RA, et al. Chronic diarrhea and pancolitis caused by paracoccidioidomycosis: a case report. Case Rep Med. 2010;2010:140505.
13. Alcántara-Figueroa C, Verástegui R, Lam MA, Cáceres-Alpaca D. Paracoccidioidomicosis colónica en un hospital de Lima–Perú: reporte de 4 casos. Rev Gastroenterol Perú. 2017;37:77-81.
14. da Cruz ER, Dal Forno A, Apratto Pacheco S, Goldmann Bigarella L, Remus Ballotin V, Salgado K, et al. Intestinal paracoccidioidomycosis: case report and systematic review. Braz J Infect Dis. 2021;25:101605.
15. Berni AD, Elias Júnior E, Arão Filho A, Paniago AM. Protein-losing enteropathy in paracoccidioidomycosis identified by scintigraphy: report of three cases. Braz J Infect Dis. 2010;14:540-3.