Case report: juvenile paracoccidioidomycosis with intestinal involvement

Relato de caso: paracoccidioidomicose juvenil com envolvimento intestinal

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ABSTRACT
Introduction: Contact of *Paracoccidioides* sp. with the human organism presents in a variety of clinical forms of the disease. Intestinal clinical manifestation is found in 10 to 30% of cases, commonly in juvenile form. This case report seeks to describe a patient with juvenile paracoccidioidomycosis with atypical intestinal involvement. Case report: A 14 years old woman with an updated vaccination schedule and no reports of chronic diseases, allergies or continued use of medications, presented a diarrheal condition that was characterized by pasty stools, where episodes became gradually more intense, associated with episodes of hematochezia, retroauricular lymphadenopathy on the right, as well as shivering and fever. A colonoscopy revealed multiple polypoid formations, ulcerations and friability throughout the colon. After biopsy results, the diagnosis of Paracoccidioidomycosis with intestinal involvement was established. Due to the wasting syndrome, anemia and persistent diarrhea, the patient was hospitalized for blood transfusion and intravenous treatment with conventional Amphotericin B. Discussion: Unlike what was presented by the patient in this case, involvement of the gastrointestinal tract is uncommon in paracoccidioidomycosis. This disease presents a range of clinical manifestations, which makes diagnosis difficult. Since this type of infection is not always considered, it may result in underdiagnosed cases, especially in women and young adults. The prognosis depends on the initial severity of the disease, the presence of comorbidities and the treatment used. Conclusion: Especially for the intestinal form, earlier treatment will better the results. The disease has a good chance of effective treatment using antifungal therapy.

Keywords: paracoccidioidomycosis, *Paracoccidioides* brasiliensis infections, delayed diagnosis, treatment.

RESUMO
Introdução: O contato de Paracoccidioides sp. com o organismo humano se apresenta em uma variedade de formas clínicas da doença. A manifestação clínica intestinal é encontrada em 10 a 30% dos casos, geralmente na forma juvenil. Este relato de caso procura descrever um paciente com paracoccidioidomicose juvenil com envolvimento intestinal atípico. Relato do caso: Uma mulher de 14 anos com um esquema de vacinação atualizado e sem relatos de doenças crônicas, alergias ou uso continuado de medicamentos, apresentou uma condição diarreica caracterizada por fezes pastosas, onde os episódios se tornaram gradualmente mais intensos, associados a episódios de hematoquezia, linfadenopatia retroauricular à direita, bem como calafrios e febre. Uma colonoscopia revelou múltiplas formações polipoides, ulcerações e friabilidade ao longo do cólon. Após os resultados da biópsia, foi estabelecido o diagnóstico de paracoccidioidomicose com envolvimento intestinal. Devido à síndrome de desperdício, anemia e diarreia persistente, o paciente foi hospitalizado para transfusão de sangue e tratamento intravenoso com anfotericina B convencional. Discussão: Ao contrário do que foi apresentado pelo paciente neste caso, o envolvimento do trato gastrointestinal é incomum na paracoccidioidomicose. Esta doença apresenta uma série de manifestações clínicas, o que dificulta o diagnóstico. Como este tipo de infecção nem sempre é

considerado, pode resultar em casos subdiagnosticados, especialmente em mulheres e adultos jovens. O prognóstico depende da gravidade inicial da doença, da presença de comorbidades e do tratamento utilizado. Conclusão: Especialmente para a forma intestinal, o tratamento mais precoce melhorará os resultados. A doença tem uma boa chance de tratamento eficaz usando terapia antifúngica.

Palavras-chave: paracoccidioidomicose, infecções por *Paracoccidioides* brasiliensis, atraso no diagnóstico, tratamento.

1 INTRODUCTION

Categorized as a disease in 1908, by Lutz, Splendore and Almeida, Paracoccidioidomycosis (PCM) is a systemic mycosis endemic to South America; mainly Brazil, accounting for over 80% of reported cases [1,2]. This condition is caused by dimorphic fungi of the genus Paracoccidioides, especially in rainy regions, with acidic and moist soil conditions [3].

Contact with the fungus is possible through transmission by inhalation, generally with predominantly pulmonary infection [4]. For the disease to develop, a transformation from the micellar form of the agent to its yeast-like pathogenic presentation takes place, which occurs at a temperature of 35 to 37°C [3].

Contact of *Paracoccidioides* sp. with the human organism presents in a variety of clinical forms of the disease, substantially affecting the lungs, aerodigestive mucous membranes (especially in the oral cavity - over 50% of cases) and skin, in its chronic form [3,5]. Although rare, intestinal clinical manifestation is found in 10 to 30% of cases, potentially occurring in children, commonly in juvenile (or acute/subacute) form, with significant lymph node involvement [3,6-9].

This case report seeks to describe a patient with juvenile paracoccidioidomycosis with atypical intestinal involvement.

2 CASE REPORT

Patient E.A.S. 14 years old, Brazilian, student, born in São Raimundo Nonato (State of Piauí), evangelical, resident and domiciled for over 13 years in the city of Jataí (State of Goiás), an urban area surrounded, in its vicinity, by non-urbanized areas and agricultural corn cultivation, attends the infectious disease department, accompanied by her mother, reporting diarrhea for the past 3 months. Patient is healthy, with no reports of chronic diseases, allergies, continued use of medications or history of previously required

blood transfusions. Exhibits mother with hypothyroidism, deceased father due to sepsis associated to paracoccidioidomycosis infection, maternal grandmother with a history of uterine cancer and aunt with a central nervous system tumor.

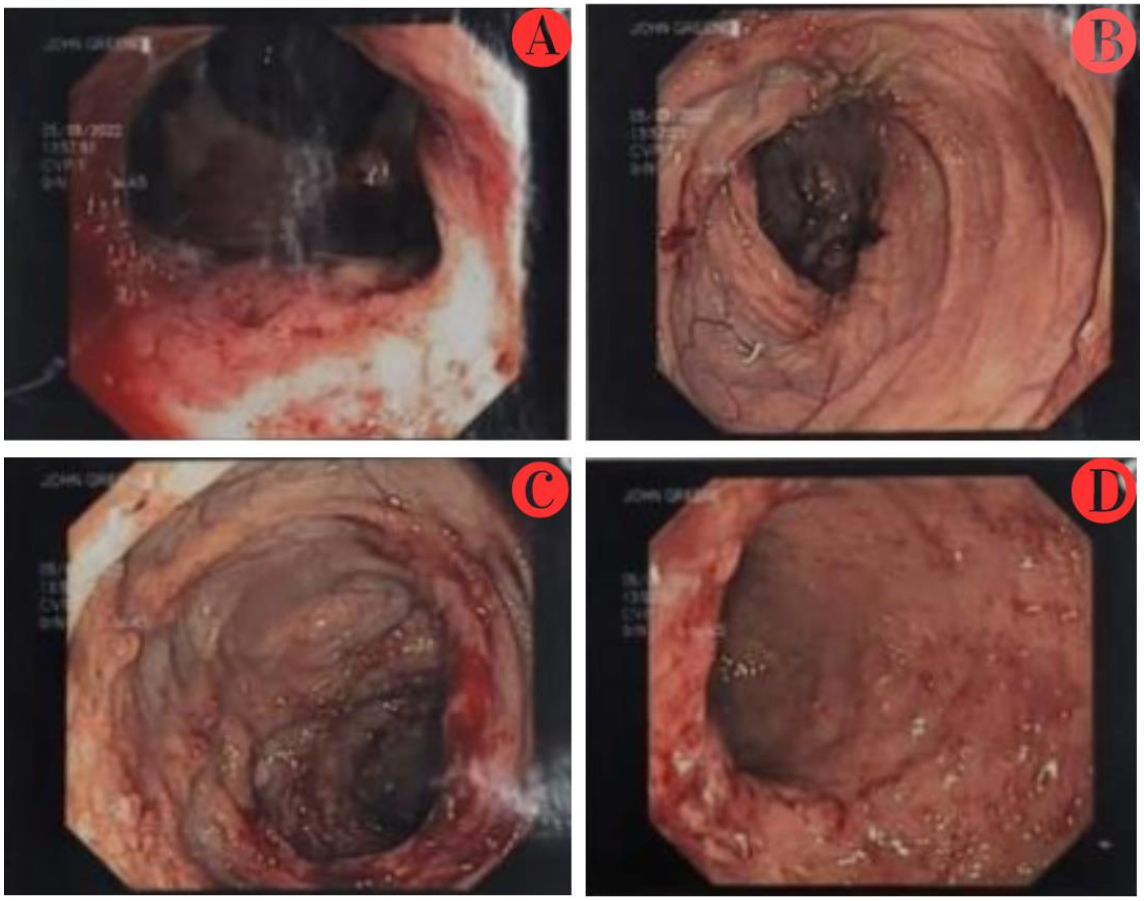
According to her mother, the diarrheal condition was characterized by pasty stools, without changes in appearance or odor, where episodes became gradually more intense, linked to an increased evacuation frequency (up to 8 episodes per day), associated with episodes of hematochezia.

Concomitant to the episode of hematochezia, the informant mentioned noticing in her daughter retroauricular lymphadenopathy on the right, as well as shivering and fever (up to 38.9 °C). She claims an updated vaccination schedule, frequent use of dewormers, menarche at 11 years old, pubarche at 10 years old and denies sexarche.

As the condition worsened, first care was provided at the Emergency Care Unit. Initial tests found hypochromic microcytic anemia, leukocytosis characterized by eosinophilia and monocytosis, as well as increased serum C-reactive protein (CRP), according to the data in table 1 (August 8th, 2022). At the time, Amoxicillin with Clavulanate was started to treat acute gastroenteritis. With this measure, added to the flora replenishers and symptomatic medications used, there was a partial response to the diarrheal episodes, however hematochezia remained.

The progressive increase in lymphadenopathy, in the cervical and inguinal regions, bilaterally, along with the persistence of other symptoms, demanded the evaluation of a proctologist doctor. A colonoscopy was performed (Figure 1), revealing multiple polypoid formations, ulcerations and friability throughout the colon, with several biopsy fragments sent to an anatomopathologist. The use of Mesalazine to treat Crohn's disease was instituted.

Figure 1. Total colonoscopy.



Legend. Images obtained through colonoscopy performed on September 5th, 2022. Evidence of stenosis and distortion of the terminal ileum, with multiple polypoid formations, ulcerations and friability throughout the colon. Furthermore, the rectum appears ulcerated, friable and with stenosis in its distal portion. A) Rectum. B) Descending Colon. C) Transverse colon. D) Terminal ileum.
Source: Patient's medical record.

After biopsy results, the diagnosis of Paracoccidioidomycosis was established. Prior to consultation with the Infectology unit, the use of Itraconazole 200 mg/day had been initiated by the proctologist, for 14 days. Consequently, there was significant improvement in diarrheal episodes, involution of lymph node chains and fistulization of postauricular lymph nodes.

The aggravation of her clinical situation, however, with discomfort, hyporexia and episodes of holocranial headaches, sanctioned the patient's transfer to the Infectious Diseases Ambulatory of a hospital unit, with less intense, though persistent, diarrhea, wasting syndrome with significant weight loss, asthenia and fistulization of the retroauricular lymph nodes, including a decrease in serum iron levels and an increase in serum CRP, according to table 1 (September 21st, 2022).

Table 1. Laboratory tests requested during the clinical investigation.
Legend. Data obtained through laboratory tests performed on August 8th, 2022, on September 21st, 2022 and on February 11th, 2022.

Test		Results	Reference interval
August 8th, 2022			
Blood Count	**Erythrocytes**	3,43 mi/mm^3	4,6-5,1 mi/mm^3
	Hemoglobin	7,3 g/dL	12,5-16 g/dL
	Hematocrit	23,6%	38-48%
	MCV	68,8 fL	78-100 fL
	MCG	21,3 pg	26-35 pg
	MCHC	30,9 g/dL	31-37 g/dL
	RDW	14%	11-15%
	Total leukocytes	19020/mm^3	5000-13000/mm^3
	Eosinophils	2282/mm^3	100-1000/mm^3
	Basophils	0	0-100/mm^3
	Typical lymphocytes	3424/mm^3	1000-5000/mm^3
	Monocytes	1131/mm^3	200-1000/mm^3
	Segmented	11792/mm^3	2000-8000/mm^3
	Platelets	419000/mm^3	150000-400000/mm^3
CRP		82,33 mg/L	<10 mg/L
September 21st, 2022			
CRP		148,24 mg/L	<10 mg/L
Serum iron		10,4 ug/dL	50-170 ug/dL
Ferritin		75,9 ng/mL	10-291 ng/mL
Fasting blood glucose		74 mg/dL	70-99 mg/dL
Urea		14 mg/dL	15-40 mg/dL
Creatinine		0,70 mg/dL	0,46-0,81 mg/dL
Potassium		4,4 mmoL/L	3,5-5,2 mmoL/L
Sodium		135 mmoL/L	136-145 mmoL/L
February 11th, 2022			
Anti-HIV		Non-reactive	

Source: Patient's medical record.

During physical examination, the patient was in a good general condition, lucid, oriented in time and space (Glasgow Coma Scale 15), acyanotic, anicteric, afebrile (37.1°C), hypocolored (+++/4). Concerning the cardiovascular system, she was normotensive, with blood pressure of 110 x 75 mmHg, heart rate of 113 bpm, regular heart rhythm in 2 beats, normophonetic sounds without murmurs.

As for the respiratory system, she demonstrated universally audible vesicular breath sounds, without abnormalities. A hypertympanic abdomen was observed, with increased hydroaerial bowel sounds, painless on superficial palpation, diffusely painful on deep palpation, and hepatosplenomegaly (liver 4 cm from the right costal margin, spleen 2 cm from the left costal margin). Moreover, visible lymph node enlargement (adenopathy) was noted in the cervical and postauricular chains; left retroauricular fistulization and predominantly right retroauricular phlogosis.

Added to this, the axillary and inguinal lymph node chains were palpable bilaterally, the oral cavity was without moriform lesions/ulcers or evidence of gingivitis. The presence of plaques adhered to the oropharynx was also not found. Additionally, the skin, skin appendages, upper and lower limbs were unchanged.

Due to the wasting syndrome, anemia and persistent diarrhea, with evidence of severe gastrointestinal involvement, the patient was hospitalized for blood transfusion and intravenous treatment of severe acute paracoccidioidomycosis with conventional Amphotericin B, reaching an accumulated dose of 325 mg. There was, thereafter, a critical clinical improvement, subsequently leading to hospital discharge and follow-up at the Infectious diseases ambulatory, with use of itraconazole 200 mg/day.

3 DISCUSSION

Unlike what was presented by the patient in this case, involvement of the gastrointestinal tract is uncommon in paracoccidioidomycosis, representing 10 to 30% of cases. As reported, this disease presents a range of clinical manifestations and impairments, which makes diagnosis difficult. Since this type of infection is not always considered, it may result in underdiagnosed cases, especially in women and young adults. The infection is predominant in men on a 15:1 ratio in relation to women and is rare in children and adolescents, being, in this age group, similar regardless of gender [3].

The risk factors for infection by this fungus are activities that involve handling soil, such as agriculture, gardening and transport of vegetable products. These epidemiological factors are important for diagnostic suspicion, especially in cases of less

typical or exuberant clinical condition [3]. As depicted, the patient lived in an urban area surrounded by non-urbanized and agricultural areas with corn cultivation, awakening clinical suspicion.

In addition to the severe acute paracoccidioidomycosis condition reported, manifestations can also be classified as subacute or chronic, with the chronic form being more common in men over 30 years of age and a prolonged clinical course of the disease[3].

It is believed that the main way for the fungus to reach an organ, such as the intestine, is via hematogenous route, but ingestion is also a possibility. About 50% of patients present oral lesions that are suggestive of PCM. They are superficial ulcers, with a granular appearance and hemorrhagic spots mainly in the upper gums, soft palate, tongue and lips. Patients without oral mucosa manifestations may have a delayed diagnosis, as was seen in this patient's case [3].

In intestinal involvement, more common in the acute and subacute form of the disease, all segments may be affected, but there is a predominance of the jejunum, terminal ileum, appendix and the proximal portion of the large intestine. Mucosa, submucosa and the abdominal lymphatic system are injured. Mesenteric nodes can undergo necrosis due to lymphatic stasis and extravasation of lymph into the intestinal lumen, causing exudative enteropathy, which can occur in the small or large intestines. In this patient, especially the terminal ileum was affected, with stenosis and distortion of the terminal ileum, in addition to polypoid formations, ulcerations and friability spread throughout the colon. Furthermore, the rectum, which in the literature is not usually affected in most cases, appears ulcerated, friable and with distal stenosis [3].

The clinical manifestations of the intestinal form are epigastric pain and diarrhea that lasts from weeks to months. Nausea, vomiting and distended abdomen are also reported. Some patients may experience abdominal pain and constipation associated with these symptoms. At the same time, there may be lesions of the oral mucosa and the presence of cervical lymphadenopathy [3]. It may also occur as bloody diarrhea, palpable masses and jaundice [1]. In this patient's case, chronic diarrhea, hematochezia, cervical, retroauricular and inguinal lymphadenopathy were observed, with no jaundice, nausea or vomiting.

Diagnostic suspicion is based on clinical and epidemiological manifestations, serology (sensitivity of 65 to 95%) and identification of the fungus. Culture, direct mycology and histopathology can be used, the latter being more common. Direct microscopic examination and histopathology are considered the gold standard. The

histopathological result shows an inflammatory infiltrate, granulomas with epithelioid cells and double-walled giant cells with simple or multiple budding, as well as pseudoepitheliomatous hyperplasia [1,3]. Furthermore, colonoscopy can be used as a complementary exam to diagnose intestinal involvement, in which ulcerations in the mucosa might be observed through visualization of the intestinal lumen[10]. The diagnosis in this case occurred after colonoscopy, when the anatomopathological study allowed confirmation of paracoccidioidomycosis.

Cases of coinfection with other pathogens and chronic multifocal forms may indicate an adjacent immunosuppressive condition, such as, for example, infection with Human Lymphotropic Virus type 1 (HTLV-1) or Acquired Immunodeficiency Syndrome (AIDS) [1,10]. In the reported case, however, there was no HIV infection.

The prognosis of PCM depends on the initial severity of the disease, the presence of comorbidities and the treatment used. Especially for the intestinal form, earlier treatment will better the results [3]. In the present case, the patient exhibits no comorbidities and the treatment instituted at diagnosis was carried out with oral itraconazole, at a dose of 200 mg/day and, due to aggravation, it was coupled with the administration of intravenous amphotericin B and continuation of the same dose of itraconazole after discharge, allowing a better prognosis.

The disease, if promptly treated, has a good chance of effective treatment using systemic antifungal therapy. Sulfonamides, azole compounds and amphotericin are used for mycological cure. Treatment duration ranges from 9 to 18 months, being one year on average. Thus, signs and symptoms can be eliminated, normalizing imaging tests and controlling weight loss. Relapses may occur, lengthening treatment [3]. In case of comorbidities, such as AIDS, antifungal therapy must be maintained for a longer period of time [1].

4 CONCLUSION

Appropriate diagnosis is essential for improving the patient's quality of life, controlling the disease and successful treatment. In the presence of intestinal symptoms and involvement resistant to treatments and accompanied by epidemiological risk factors, adequate etiological investigation is important to determine causation and to eliminate differential diagnoses.

Therefore, it's important to map the origin of patients presenting the disease, in order to have better control through targeted decision-making, aside from the necessity to stress the importance of properly following treatment to patients and health professionals.

ETHICAL CONSIDERATION

The use of data to prepare this case report was approved by the Research Ethics Committee of the Federal University of Jataí (CEP/UFJ) with the protocol number 6.304.867, in accordance with CNS Resolutions 466/12 and 510/16.

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