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CASE REPORT

Disseminated juvenile paracoccidioidomycosis evolving with portal hypertension: a case report

Paracoccidioidomicose juvenil disseminada evoluindo com hipertensão portal: um relato de caso

Taciana de Souza Bayão[1,2], Giovanna Barille[1,2], Lucas Rodrigues Diniz[1,2], Cláudia Biasutti[1,2], Aloísio Falqueto[1,2]

[1] Universidade Federal do Espírito Santo. Vitória/ES, Brasil.

[2] Hospital Universitário Cassiano Antonio Moraes. Vitória/ES, Brasil.

E-mail:
tacianadesouzabayao@gmail.com

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ABSTRACT

Introduction: Juvenile paracoccidioidomycosis (PCM), a disease caused by fungi of the genus *Paracoccidioides*, requires high clinical suspicion, as a range of differential diagnoses are possible. **Case report:** This report describes a patient diagnosed with juvenile PCM who, due to low adherence to treatment, developed a more extensive fungal invasion within eight years, causing portal hypertension due to portal vein thrombosis. This is a rare and serious manifestation. **Conclusion:** Only six similar reports were identified in the medical literature, through a search in the databases of the *Pubmed* and *Scielo* platforms.

Keywords: Paracoccidioidomycosis; Portal hypertension ; Paracoccidioides.

RESUMO

Introdução: A paracoccidioidomicose juvenil (PCM), doença causada pelos fungos do gênero *Paracoccidioides*, exige alta suspeição clínica, já que uma gama de diagnósticos diferenciais é possível. **Relato de caso:** Neste relato é descrito um paciente com diagnóstico de PCM forma juvenil que devido à baixa adesão ao tratamento evoluiu em oito anos para uma invasão fúngica mais extensa, ocasionando hipertensão portal por trombose de veia porta. Esta é uma manifestação clínica rara e grave. **Conclusão:** Foram identificados somente seis relatos similares na literatura médica, por meio de busca nas bases de dados das plataformas *Pubmed* e *Scielo*.

Palavras-chave: Paracoccidioidomicose; Hipertensão portal; Paracoccidioides.

INTRODUCTION

Paracoccidioidomycosis (PCM) is a systemic fungal disease caused by different species of microorganisms belonging to the genus *Paracoccidioides*. Until the beginning of the 21st century, *Paracoccidiodes brasiliensis* was considered the only species causing PCM. Currently, *P. lutzii, P. brasiliensis sensu stricto, P. americana, P. restripsiensis* and *P. venezuelensis* are the known species in the genus Paracoccidioides[1,2].

The disease is endemic to Central and South America. The incidence of PCM in Brazil varies from 1 to 4 cases for every 100,000 inhabitants per year in endemic locations in the Southeast and South regions. Human beings are mainly infected in the field, during agricultural activities. Rural workers between 30 and 60 years old are the population with the highest incidence of the disease, with a ratio of twenty men for every one woman affected[1,3].

The juvenile PCM, also called acute/subacute, is described in less than 20% of patients. We describe below a case of a patient diagnosed with juvenile form of PCM which due to low adherence to treatment, evolved over eight years into a more extensive fungal invasion, causing rare forms of disease presentation.

CASE REPORT

Male, rural worker, non-smoker and non-drinker, born and resident in a rural area of Espírito Santo - Brazil, was referred to the outpatient clinic of the Hospital Universitário Cassiano Antonio Moraes (HUCAM/UFES) in May 2015, at the age of 23. At the time, he reported six months of feverish peaks, adynamia and weight loss of 7kg. On physical examination, he was edematous, with lesions in the oral cavity, skin ulcers on the face, cervical and inguinal lymphadenopathy, as well as non-painful hepatosplenomegaly (Figure 1).

At that time, serology for aspergillosis, histoplasmosis, HIV, syphilis, hepatitis B and C, and antigen testing for cryptococcosis were negative. Tests for tuberculosis (AFB and culture for Mycobacteria) in the lymph node were also negative. CT (Computed tomography) scans of the neck, chest and abdomen in 2015 showed multiple adenomegaly and hepatosplenomegaly with preserved echotextures. The diagnosis of PCM was made through cervical lymph node aspirate with visualization of yeasts characteristic of *Paracoccidioides sp*. (Figure 2), was initiated

FIGURE 2. Multiple budding yeasts observed on direct mycological examination of cervical lymph node aspirate

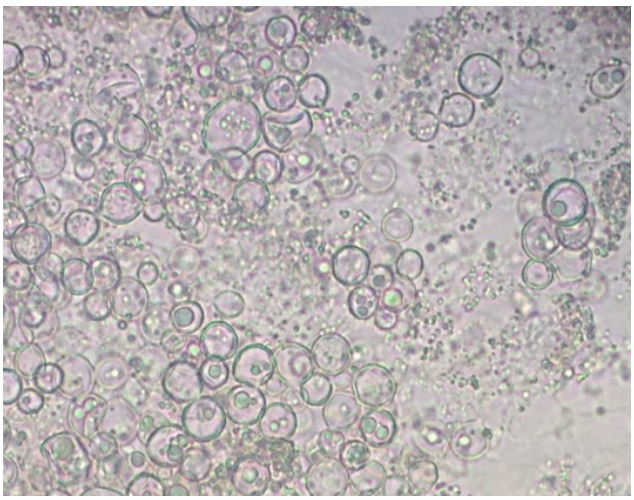

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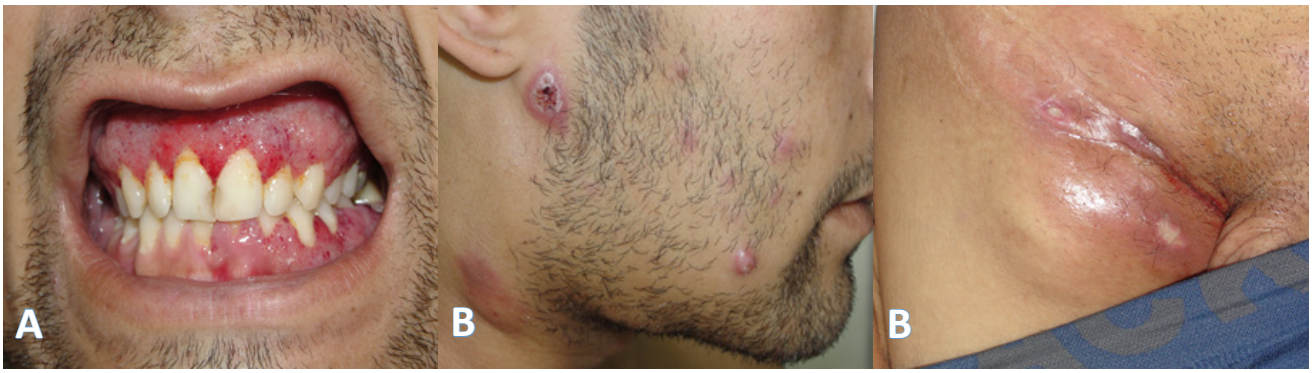
FIGURE 1. Juvenile form (acute/subacute) of PCM A- Gingivostomatitis B- Multiple fistulized lymph nodes in the cervical, submandibular and inguinal chains

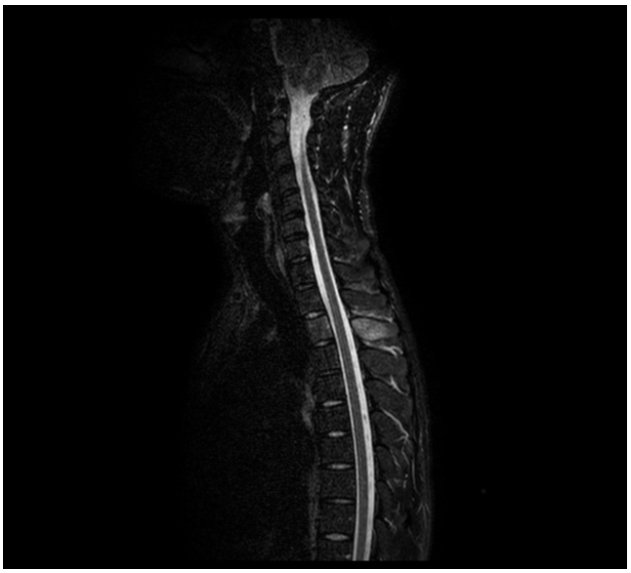


Source: Authors.

for 4 weeks treatment with liposomal amphotericin B at a dose of 5 mg/kg/day.

The patient presented a satisfactory response and maintenance was carried out with an oral prescription of Sulfamethoxazole + Trimethoprim. However, due to poor medication adherence, there were several returns for outpatient consultations where the patient was symptomatic. In 2018, he complained of inflammatory thoracic lumbosacral pain, and bone involvement by PCM was identified through imaging (Figure 3).

FIGURE 3. Spine magnetic resonance imaging (MRI) in November-2018: infiltrative bone lesions, short tau inversion recovery (STIR) sequence demonstrating involvement of the third thoracic vertebra



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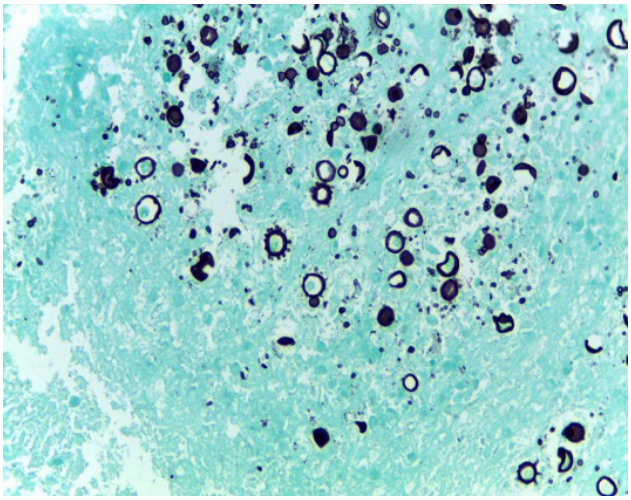
In December 2021, he suffered abdominal trauma, requiring an emergency splenectomy. In the histopathological examination of the spleen, an abscess measuring approximately 6cm was identified, with the fungus visible in this organ (Figure 4).

In July 2022, he developed intense dyspnea with a massive pleural effusion on the right. At that time, the rapid molecular test, AFB and pleural fluid culture were positive for tuberculosis, as well as the direct test for sputum fungi positive for PCM, therefore, the RHZE regimen was started in addition to a new cycle of amphotericin. In October 2022, the patient was readmitted to the hospital with massive ascites, with laboratory analysis of abdominal fluid suggesting portal hypertension (serum albumin gradient and ascitic fluid albumin: 2.06 | protein: 0.53)

FIGURE 4. Histological section of the spleen stained by the Grocott method with yeast cells from the Paracoccidioides sp. in organizing granulomas and suppurative infiltrates



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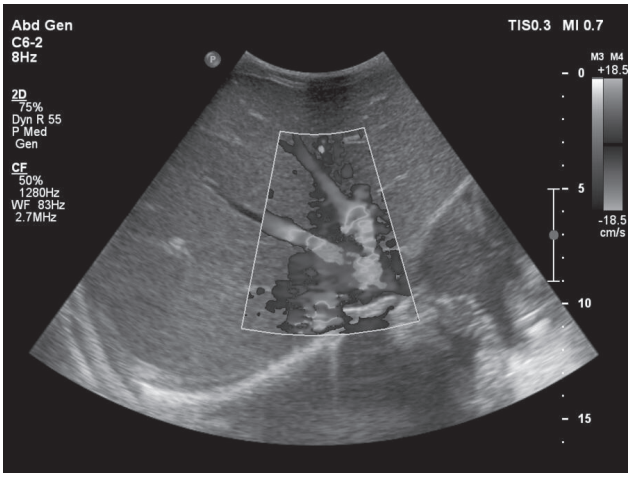
with exclusion of etiology alcoholic, autoimmune and other infections such as peritoneal tuberculosis. Sequential testing for microorganisms in feces was also negative. Upper digestive endoscopy (15/09/2022) demonstrated moderate hypertensive gastropathy, and tomography of the abdomen and pelvis (15/09/2022) showed an increase in the amount of free intra-abdominal fluid, with liver shape, contours and dimensions normal, without evidence of focal lesions. Abdominal USG with Doppler (09/23/2022) identified portal vein thrombosis (Figure 5). In this context, the cause of portal hypertension was attributed to the diagnosis of PCM.

FIGURE 5. Ultrasound imaging (USG) of the upper abdomen in September-2022: cavernomatous transformation of the portal vein (signs of old thrombosis)



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It is observed that throughout the years 2015, 2018, 2021 and 2022, several treatment attempts were made with cycles of liposomal amphotericin B, in doses between 50 and 100 mg/kg. However, there were several moments of treatment abandonment, whether due to poor adherence, imprisonment in the prison system between 2016-2020 or difficulty accessing the health service.

In November 2022, the patient is admitted to the ICU due to respiratory failure secondary to bilateral pleural effusion and severe malnutrition. In December/2022, eight years after the diagnosis of the disease, he died.

DISCUSSION

Juvenile PCM is a clinical form that affects men and women equally, mainly children and young adults. Once inhaled in the form of a conidium, the fungus reaches the lower airways, leading to the activation of the local inflammatory cellular response. A robust Th1 immune response composed of neutrophils and macrophages prevents the spread of this microorganism. When the infection is not promptly contained, it evolves into a systemic disease within weeks to months after exposure, constituting juvenile PCM[1,4].

The individual who becomes ill from juvenile PCM usually presents lymphadenopathy with eventual suppuration, skin lesions, fever and anorexia. Clinical suspicion for PCM should be high, especially in endemic regions, as a range of differential diagnoses are possible, such as infections by viruses, mycobacteria and other fungi[2,4].

This present study demonstrates a case of portal hypertension caused by PCM. This is a rare and serious manifestation. Six reports were identified in the medical literature, through a search in the databases of the *Pubmed* and *Scielo* platforms, with the following descriptors: "paracoccidioidomycosis" + "portal hypertension". Among these cases, we highlight that one individual was coinfected with schistosomiasis and the other with hepatitis C, diseases classically described as causes of portal hypertension[4,5]. Furthermore, hepatic involvement by PCM is also described in the medical literature as a consequence of perihepatic lymph node obstruction, inflammatory ductal fibrosis or even periampullary obstructive lesion, resulting in jaundice due to cholestatic syndrome[4,5,6,7,8,9,10]. The rare cases that indicate this clinical manifestation highlight the importance of the differential diagnosis of PCM with proliferative diseases and periampullary tumors.

The patient in our clinical report had no history of alcoholism nor positive antibodies to autoimmune diseases. His viral serologies collected annually were negative, as were the negative stool tests in multiple samples, ruling out hypotheses such as schistosomiasis. In this patient, the anatomy of the bile ducts had an anatomical appearance and the liver did not appear cirrhotic, data observed in abdominal tomography scans performed over the eight years of PCM evolution. The evidence of portal hypertension secondary to portal vein thrombosis is corroborated by the USG of the abdomen with Doppler performed in September 2022, indicating the cavernomatous transformation of the portal vein. The histopathological evaluation of the spleen, carried out in 2021, already suggested this complication. However, we emphasize that liver biopsy would be the gold standard test in case of diagnostic doubt[2,5].

Another relevant fact in this report is bone invasion by PCM, which should always be remembered when complaining of acute/subacute low back pain. Osteoarticular involvement is rare, estimated to occur in less than 20% of patients with disseminated PCM, making it necessary to exclude other possible diagnoses such as bone tuberculosis. Bone injuries reported in the medical literature are mainly in the chest and shoulder girdle. Lesions in the spine are rarely described, they affect the vertebral bodies and extend to the pedicle[1,11].

Furthermore, the patient also presented, concomitantly with systemic mycosis, pleural involvement by *Mycobacterium tuberculosis*, as in addition to severe immunosuppression caused by the underlying disease, he also presented another important epidemiological factor: being deprived of liberty[1,2]. It is estimated that almost 20% of individuals diagnosed with PCM may develop tuberculosis together[1,2,3,12].

Therefore, the present clinical case demonstrates a prolonged evolution of the juvenile form,

leading to severe immunosuppression lasting over eight years and resulting in death. It is noteworthy that *Paracoccidioides sp*. are sensitive to sulfonamides, azoles and amphotericin B. To treat infection caused by these microorganisms, antifungals such as itraconazole and clotrimazole are used for mild/moderate forms. Amphotericin B, on the other hand, is reserved for severe or persistent forms, with the liposomal presentation being better indicated, due to lower toxicity[1]. Thus, despite several treatment attempts made in this patient, it is likely that both the recurrent abandonment of therapies and the state of advanced immunosuppression associated with tissue fibrosis caused by the fungus contributed to a degree of tolerance to treatment with amphotericin B. We emphasize that no solid evidence is found in the medical literature to support primary or secondary resistance of the fungus to the recommended antifungals[1,2,4].

CONCLUSION

PCM is a systemic mycosis with high morbidity, mainly due to late diagnosis. The deaths are related to the spread of the disease, leading to respiratory failure and adrenal insufficiency. As it does not require compulsory notification, we do not have data on its real incidence and prevalence in our country[1,2]. It is urgent to expand the scientific production of epidemiological data, diagnoses and treatments on this neglected tropical disease, in order to provide health improvements for populations. Furthermore, therapeutic adherence is essential for the success of treatment. Analysing the current context of PCM and the outcome of our patient we suggest, at a public health level, the organization of a treatment control program for PCM, in a similar way to what already exists for tuberculosis and can even coexist in the same centers.

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DECLARATIONS

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Author Contributions

Design: ABC, DEF, GHI. Research: ABC, DEF, GHI. Methodology: ABC, DEF, GHI. Data collection: ABC, DEF, GHI. Data processing and analysis: ABC, DEF, GHI. Writing: ABC, DEF, GHI. Revision: ABC, DEF, GHI. Approval of the final version: ABC, DEF, GHI. Supervision: ABC, DEF, GHI.

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Conflict of Interest

The authors declare no conflicts of interest.

Ethics Committee Approval

This study was approved by the Research Ethics Committee, under the CAAE number 70430023.7.0000.5071 of the Federal University of Espírito Santo (UFES).

Availability of Research Data and Other Materials

Research data and other materials can be obtained by contacting the authors.

Responsible Editors

Carolina Fiorin Anhoque, Blima Fux.

Correspondence Address

Rua Doutor Vicente Bretas Cupertino, 384, casa, Centro, Santo Antonio do Grama/MG, Brasil. CEP: 35388-000.