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Case Report

Paracoccidioidomycosis differential diagnosis: case series

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Abstract: Paracoccidioidomycosis is a neglected disease and the most important systemic mycosis in Latin America. This fungal infection is directly linked to activities related to the rural environment, such as agriculture. Despite being a frequently diagnosed disease in Brazil, the real rates of prevalence and incidence are not estimated due to the non-mandatory notification of the disease, which was recently implemented in 2020. We report three interesting cases of Paracoccidioidomycosis in immunocompetent adults, with varied clinical manifestations.

Keywords: *Paracoccidioides* sp.; Paracoccidioidomycosis; Systemic mycosis; Diagnosis; Brazil.

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1. Introduction

Paracoccidioidomycosis (PCM) is a systemic mycosis restricted to Latin America and occurs mainly in tropical areas of Brazil, Argentina, Colombia, Ecuador, and Venezuela [1]. This disease is more prevalent in adult men who perform agricultural activities. Currently, there is an increasing number of cases in urban areas with a greater representation in females [2].

The etiological agents are classifield in the Paracoccidioides brasiliensis complex [3]. Infection can produce acute disease, or the fungus can remain dormant and manifest itself after a few years. The chronic disease manifests by pulmonary involvement and the presence of ulcerated lesions on the skin and mucousa [4-6]. Definitive diagnosis of PCM is obtained by direct observation or culture of the fungus [1]. The Itraconazole (200 mg daily for 9-12 months) is the best treatment option for mild to moderate clinical forms of the disease and Cotrimoxazole (trimethoprim-sulfamethoxazole) for 18-24 months is the main therapeutic alternative to Itraconazole. A short (2–4 weeks) induction therapy with Amphotericin B (AmB) is reserved for severe cases of the disease [7].

In this study we describe a series of patients diagnosed with PCM in an endemic area of in Brazil.

2. Case Report

2.1 Case 1

In July 2021, a 19-year-old healthy black female ballet dancer presented with cervical and inguinal lymph node enlargement associated with asthenia, low-grade fever, and progressive weight loss. The computed tomography (CT) scan indicated the presence of fluid in the pelvic cavity, and inguinal lymphadenopathy. In May 2022, the diagnosis of the patient was not yet confirmed. In this period, vesicular and crusted lesions appeared

on the upper limbs and face, accompanied by intense abdominal pain, nausea, and progressive lymph node enlargements (supraclavicular, retroauricular, axillary, inguinal and abdominal).

On the 23rd of May (2022), the patient was admitted to a general hospital, and she continued to experience worsening of abdominal pain. The forehead lesion evolved with the formation of confluent crusts, pustules, and ulcerations, forming a single painful plaque. On the 23rd of July (2022), which is a year after the onset of symptoms, the patient was transferred to a university hospital. The culturing of cervical lymph node aspirates and fragments of facial lesions confirmed the growth of *Paracoccidioides* sp. On 30th July (2022), patient treatment was initiated with Itraconazole (200 mg/day for 4 days) and replaced after 4 days with Liposomal AmB (3mg/Kg/day for 25 days).

Complementary treatment with Itraconazole (200mg/day) was scheduled for a period of six months. The patient was discharged from the hospital on 5th September (2022) with improvement of both the skin lesions on the face and clinical symptoms. During hospitalization, she had developed moderate anemia and leukocytosis, but laboratory tests were normal at discharge. Figure 1 shows the main lesions and signs presented during the course of the disease.

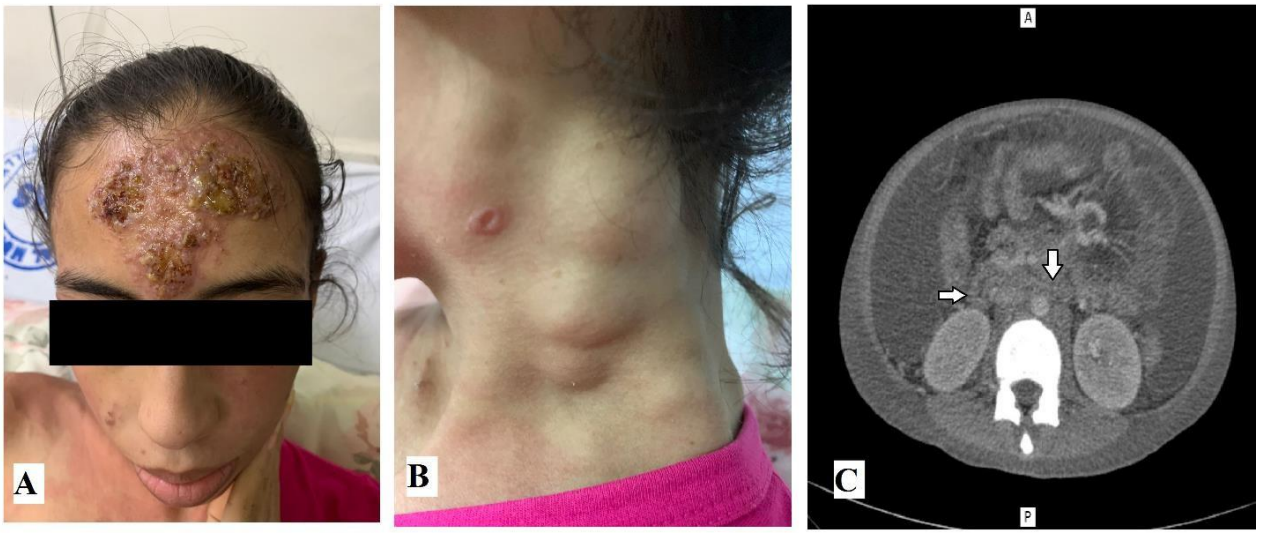

Figure 1. Patient with PCM juvenile-type. A - confluent crusted lesions on the forehead. B - Exuberant lymph node enlargement in the cervical region. C - Presence of lymph node enlargements in the abdominal cavity (CT scan).

On 19th of October (2022), the patient was hospitalized for the second time (44 days after hospital discharge) with nausea, vomiting and severe abdominal pain. Abdomen CT scan showed a cluster of necrotic lymph nodes in the abdominal cavity, causing an obstructive process in the mesenteric vein, and partial necrosis of the spleen. The patient was immediately placed on treatment with Itraconazole, after which on the 7th of November (2022), treatment with Liposomal AmB (5mg/kg/day) was initiated and continued for 28 days. The patient was discharged from the hospital with considerable improvement, and continued treatment with Cotrimoxazole (trimethoprim-360mg/sulfamethoxazole-1600mg a day), with an expected duration of treatment of two years.

2.2 Case 2

This case presents a 76-year-old retired female housewife with a history of Systemic Arterial Hypertension, Type 2 Diabetes and Hypothyroidism. The patient is often involved in gardening activities in the backyard of her house in an urban region of the city,

Niteroi (State of Rio de Janeiro). In June 2022, the patient presented with clinical manifestations of dyspnea on moderate exertion, recurrent symptoms of colds and the appearance of ulcerated lesions on the lower lip and oral mucosa. Chest CT scan showed disseminated micronodules in the lungs, with 75% involvement. Direct microscopy examination of the oral mucosal lesion fragments confirmed the presence of diagnostic structures of PCM.

On 20th October (2022, which is 4 months after the onset of symptoms), the patient was hospitalized and treatment with Itraconazole (200mg/day) was started on 31st October 31 (2022). The patient displayed significant weight loss due to difficulties (pain) in chewing and swallowing food caused by the lesions in the oral cavity. After 12 days of hospitalization, the patient was discharged on 1st November (2022).

The oral lesions healed, and the patient's respiratory capacity improved considerably. Treatment with Itraconazole was scheduled for a duration of 9 months, during which she was monitored through outpatient visits. Lung lesions are likely to constitute permanent sequelae, requiring drug support for obstructive pulmonary diseases. Figure 2 shows the lesions of the oral cavity and the patient's pulmonary radiological image.

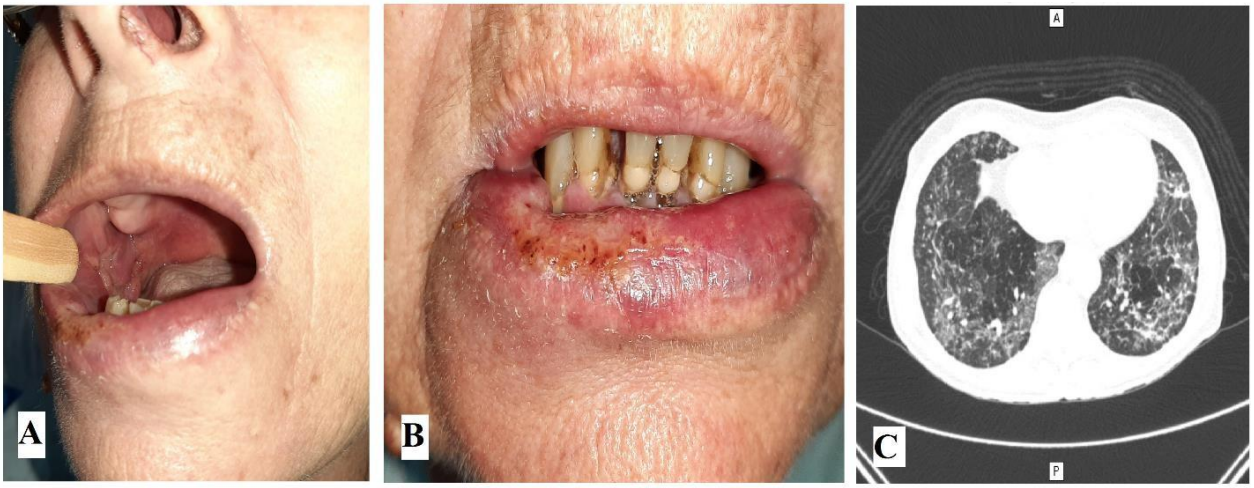

Figure 2. An elderly woman with Classic PCM adult-type. A and B - oral involvement with ulcers and hemorrhagic dots. C – Chest CT scan shows irregular cavitary areas of enhancement associated with parenchymal distortion and paracicatricial emphysema.

2.2 Case 3

This case is about a 64-year-old artisan man, healthily born in São Gonçalo, Rio de Janeiro. His daily activities involve manually extracting bamboo to make handcrafted furniture. On 10th June (2020), the patient experienced sudden vertigo, moderate disorientation, dysphagia, and paresthesia of the right half of the body. Nuclear Magnetic Resonance performed on the 19th June (2020) and CT scans of the brain on the 23rd June (2020) showed an oval, heterogeneous, multiloculated, contrast-enhanced lesion in the left parietal region of the brain.

Nineteen days after the onset of symptoms, the patient was hospitalized for diagnostic investigation. Chest CT scan taken on 1st July (2020) showed widespread reticulonodular lesions in both lungs. Both serological and diagnostic tests were negative for HIV and tuberculosis, respectively. On 28th July (2020, 49 days after the onset of symptoms), surgery was performed to remove the brain lesion and the procedure was successfully performed. Histopathological examination of brain tissue showed rounded structures consistent with the diagnosis of paracoccidioidomycosis. Direct examination for fungi was positive.

Treatment with Liposomal AmB (5mg/kg/day) was performed for 14 days, which was then replaced with Cotrimoxazole (trimethoprim-480mg/sulfamethoxazole-2400mg a day) until the patient was discharged from the hospital. The patient was hospitalized

for 68 days, after which there was a complete resolution of neurological symptoms, but he continued to experience respiratory distress on moderate physical exertion. The Cotrimoxazole was continued for more than two years (until October 2022), with outpatient medical follow-up. No new brain lesions appeared, and residual lung lesions stabilized without compromising the patient's respiratory capacity. Figure 3 shows the main radiological findings during hospital stay.

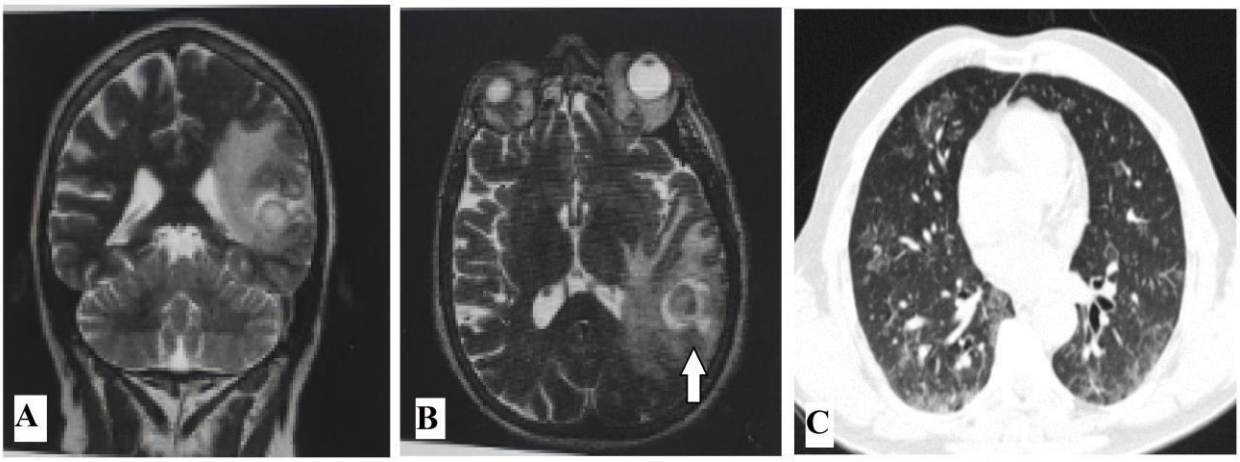

Figure 3. Chronic PCM in an elderly man. A – Brain MRI showing hypoattenuating lesion. B - Brain MRI showing hypoattenuating lesion with hyperattenuating halo, causing mass effect in the left parietal lobe. C – Chest CT scan shows lungs with irregular micronodules in a random distribution.

3. Discussions and conclusions

We report three interesting cases of PCM in patients from urban regions. Case 1 presented the juvenile type, without pulmonary involvement, but serious involvement of lymph nodes and skin integument. Case 2 describes the classic chronic form, with varying degrees of lung and oral mucosa lesions. Case 3 also describes a chronic form, but that is very unusual because it started with sensorineural symptoms.

Diseases such as leishmaniasis, sporotrichosis, histoplasmosis, skin cancer and vasculitis should be considered as a differential diagnosis for the cutaneous-mucosal PCM [8]. It is important to observe the concomitance of mucocutaneous lesions and adenopathy's, forming a triad of symptoms characteristic of this disease. In the first case reported, the skin lesion was directly related to severe lymph node involvement, raising high suspicion of the diagnosis of PCM.

Juvenile-type PCM is the most severe clinical form of this mycosis, with a tendency to spread through lymph nodes, liver, spleen, and bone marrow, resulting in many complications, including death [4]. This clinical presentation strongly compromises the mononuclear phagocytic system, without pulmonary involvement [9]. The young woman in Case 1 had a significant consumptive syndrome and massive adenopathy, progressing to a very serious presentation of the disease with poor prognosis. The significant involvement of cervical lymph nodes raised an important suspicion of tuberculosis or lymphoma during the investigation phases of the case.

The chronic form of PCM has a variable clinical presentation and can compromise several organs and systems, and mainly affects men (male: female ratio of up to 22:1) in the range of 30 to 59 years old [10]. The lungs are involved in more than 90% of the cases. However, central nervous system (CNS) involvement is reported in 10 to 27% of the cases and is mainly associated with pulmonary manifestations of the disease [11,12]. Both cases of chronic disease reported in this manuscript had disseminated lung lesions, with repercussions on the patients' respiratory capacity (permanent sequelae). The PCM should be included in the differential diagnosis of the Chronic Obstructive Pulmonary Disease in endemic regions.

Sometimes, neurological symptoms are the first manifestations of disseminated PCM. The main symptoms are headache, seizures, focal weakness, and gait disturbances. Signs of increased intracranial pressure may also be found [13]. In Case 3, neurological symptoms were the first manifestations of the disease, raising the possibility of cerebrovascular disease or brain cancer. The surgical intervention was performed successfully to avoid the patient's death, and essential to avoid the emergence of new brain lesions.

Atypical and severe forms of PCM have been reported in patients with immunosuppressed HIV infection [12]. The patient in case 3 had symptoms very similar to those classically produced by cerebral toxoplasmosis, constituting a diagnostic hypothesis.

Currently, estimating the true prevalence of PCM is a very difficult task because it is still a neglected disease. In regions considered endemic such as Brazil, the diagnosis of PCM should be considered in lung, lymphatic, mucosa, cutaneous and central nervous system diseases. Due to the long latency period of PCM, the active search for cases and adequate treatment is very important to avoid chronic sequelae and possible lethal outcomes.

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Research Ethics Committee Approval: Three patients diagnosed with PMC were followed at the Antonio Pedro University Hospital. Written informed consents were obtained from all patients. The local ethics committee reviewed and approved the study and assigned the approval number: CAAE: 64792722.0.0000.5243.

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Conflicts of Interest: The authors declare no conflict of interest.

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