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CASE REPORT

Paracoccidioidomycosis with fatal outcome in a patient from the Brazilian Pantanal: a case report

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Abstract

Objective: To report a severe, late diagnosed case of paracoccidioidomycosis in a 12 year-old boy with fatal evolution and positive lymph node biopsy for the fungus, and to conduct a literature review on the disease. **Comments:** we have highlighted the importance of differential diagnoses, even if this disease is rare in certain age groups, as well as the need of clinical investigation at the onset of symptoms and the inefficiency of late treatment.

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INTRODUCTION

Paracoccidioidomycosis is a systemic mycosis first described in 1908. It is native to Latin America, with the highest incidence in South America. In Brazil, most cases have been reported in the South, Southeast, and Central-West regions. It is endemic to rural areas, affecting mainly males aged 30-60 years.

It occurs less frequently under 14 years of age, an age group in which there is no sex predominance. Although it rarely occurs in pediatric patients and presents a low-specificity clinical picture, common to other diseases, its diagnosis is usually late. The etiologic agent is the thermally dimorphic fungus *Paracoccidioides brasiliensis*[1,2].

The acute/subacute form (juvenile or adolescent) is the clinical form of the disease until 30-35 years of age. It accounts for 3%-5% of cases and features superficial and deep lymphadenomegalies; suppuration of ganglionic masses; hepatosplenomegaly; and digestive, skin, and osteoarticular symptoms, in addition to anemia, fever, and weight loss. The lungs are rarely involved[1-4].

The unifocal/multifocal chronic adult form of the disease is more common (90% of the cases), with a predominance in men. It has chronic progression, and symptoms of weakness, weight loss, fever, cough, and shortness of breath predominate[1-4].

The gold standard of diagnosis is the identification of the fungus in fluid samples or tissue biopsies. Serological tests are important aids to diagnosis, and they also evaluate the response to treatment and the relapses. Imaging examinations, such as chest X-rays and computed tomography (CT) scan, show findings suggestive of the presence of the fungus and also aid the diagnosis[1-4].

Treatment includes support measures for clinical complications and specific antifungal therapy. Patients should be monitored until they meet the criteria for cure. *P. brasiliensis* is sensitive to most antifungal drugs, including sulfonamides. Therefore, several antifungal drugs, such as amphotericin B, sulfonamides (sulfadiazine, trimethoprim/sulfamethoxazole), and azole antifungals (ketoconazole, fluconazole, itraconazole), can be used to treat these patients[4].

CASE REPORT

A male patient (F.S.C.) aged 12 years 11 months, of a mixed-race (African and Caucasian), from the town of Ladário, State of Mato Grosso do Sul, Brazil, was admitted to the pediatric ICU with a history of shortness of breath, initially on heavy exertion, with progressive worsening, pallor, and prostration within 2 months. He denied other symptoms prior to hospital admission. In the week prior to admission, jaundice and ascites appeared. He reported a loss of 14 kg in this period and widespread skin lesions (described as crusty) at the beginning of the clinical picture.

He was previously healthy and lived in a rural area in the Pantanal wetland region, and he used to help his father in agriculture. Initial physical examination revealed that he was emaciated, pale, with generalized lymphadenomegaly, reduced breath sounds in the left hemithorax, round and distended abdomen, and positive fluid wave test.

A chest X-ray evidenced a left pleural effusion; thoracentesis was performed, but it did not meet Light's criteria for identifying exudates. Paracentesis was performed to drain 360 mL of ascitic fluid, SAAG < 1.1. An echocardiogram showed a discrete pericardial effusion.

At admission, laboratory tests indicated anemia, leukocytosis with a shift to the left, increased inflammatory activity, and cholestasis Tables 1 and 2.

Table 1. Laboratory tests

Biochemistry and cellularity - pleural effusion	
pH	7.0
Leukocytes	3,808
Lymphomononuclear	87
Polymorphonuclear	13
Red blood cells	53,000
Glucose	78
Proteins	3.7
LDH	107
Chloride	97
Biochemistry and cellularity - ascitic fluid	
pH	8.0
Leukocytes	417
Lymphomononuclear	90
Polymorphonuclear	10
Red blood cells	8,000
Glucose	71
Proteins	3.0
LDH	71

CT scan showed the following: left-sided hydropneumothorax; left pleural effusion leading to atelectasis by hypoexpansion; prominence of the right lung hilum with oval hypodense areas; enlarged lymph nodes in the axillary and cervical-thoracic chains; presence of a few rounded osteolytic images in the humeri, sternum, and ilium wings; massive ascites; marked splenomegaly with sparse, oval, focal, hypodense areas spreading through the parenchyma; enlarged lymph nodes of increased dimensions in the left para-aortic area, inter-aortocaval area, and at the mesenteric root; and slightly enlarged liver with homogeneous density.

Since admission, the patient also presented hypercalcemia and increased LDH and creatinine levels.

Table 2. Laboratory tests (continuation)

Laboratory tests	
Hemoglobin	7.4
Hematocrit	22.8
Leukocytes	16,600
Metamyelocytes	2
Band cells	23
Segmented cells	67
Lymphocytes	2
Monocytes	3
Eosinophils	3
Platelets	182,000
Total bilirubin	5.96
Direct bilirubin	5.07
Total protein	7.6
Albumin	1.0
Alkaline phosphatase	691
Ultra-sensitive CRP	22.14
Calcium	12.4
LDH	2,008
Creatinine	1.38

The hypothesis of neoplasm was raised, and bodily fluids were sent for histopathological analysis. A CT scan of the thorax, abdomen, and pelvis was performed.

Antibiotic therapy was started with cefepime, and later teicoplanin, micafungin, meropenem, and sulfamethoxazole with trimethoprim were also included.

The patient progressed 48 hours after admission with decreased consciousness, requiring orotracheal intubation. During the intubation procedure and the feeding tube placement, there was profuse bleeding from the esophagus and trachea. Esophageal candidiasis was also observed.

A biopsy of the lymph nodes and a myelogram were performed 72 hours after admission. The patient died on that same day.

The biopsy result was obtained 5 days after the death. The diagnosis of paracoccidioidomycosis was confirmed. On microscopy, the histological sections of the lymph nodes showed an altered tissue structure, owing to the proliferation of histiocytes and a few multinucleated giant cells, as well as polymorphonuclear infiltrate with intracytoplasmic refringent yeast-like structures. Special staining revealed buddings and differences in size between the shapes.

The bone marrow biopsy reinforced the diagnosis, showing fungal infestation by yeast-like structures compatible with *P. brasiliensis*.

DISCUSSION

Paracoccidioidomycosis or Lutz-Splendore-Almeida disease is a systemic mycosis that is disseminated through the blood and lymph and is caused by the saprophytic fungus from plants and soil *Paracoccidioides brasiliensis*. It is endemic in rural areas, particularly in the South, Southeast, and Central-West regions of Brazil. It is a granulomatous disease of insidious progression[1,2,5]. The difficulty of access to health care services as well as lack of information among the affected population may delay the diagnosis.

Dissemination occurs through the inhalation of particles, with the respiratory tract being the gateway into the body for the fungus. From there, the fungus can spread through the blood or lymph. All organs of the body can be affected, with the lungs, lymph nodes, adrenal glands, bones, digestive tract, and nervous system being the most frequently affected[5].

The disease is classified into five forms, according to the International Colloquium on Paracoccidioidomycosis (1986) and the Brazilian Consensus in Paracoccidioidomycosis: infection, disease (acute, subacute, and chronic forms), and residual[1,2].

The acute form of paracoccidioidomycosis, the juvenile type, typically occurs in young patients of both sexes and is characterized by tropism of the fungus to the mononuclear phagocytic system[3].

It is clinically characterized by superficial- and deep--chain lymphadenomegaly, associated with involvement of the liver, spleen, and bones. The initial clinical picture is similar to Hodgkin's lymphoma, with hard and coalesced lymph nodes, associated with evening fever. Without treatment, the lymph nodes become inflamed and suppurate and form fistulas. Skin lesions are frequent, but lesions of mucous membranes are rare. The spread of the fungus through the lymph and blood leads to increase in the mortality rate[3]. The patient in the present case had generalized lymphadenomegaly and liver, spleen, and bone involvement.

Direct mycological examination is a highly effective and low-cost method of screening for the fungus, being considered the gold standard. Sputum, scrapings from cutaneous lesions or from mucosae, lymph node aspirate, and material obtained through fiber-optic bronchoscopy can be used[1,4].

A chest X-ray can show a reticulonodular infiltrate, predominantly in the two upper thirds of both lungs, asymmetrical, with hypertransparency at the lung bases. A CT scan can show nodules, ground-glass opacity, tree-in-bud sign, acinar lesions, parenchymal bands, peribronchovascular interstitial thickening, cavities, reticular patterns, reversed halo sign, paracicatricial emphysema, and traction bronchiectasis[1,4].

CNS involvement is characterized by two forms: the meningeal form (chronic leptomeningeal inflammation, distributed focally at the base of the skull) and the granulomatous

or pseudotumor form (multiple, random nodular lesions with peripheral, ring-shaped contrast impregnation)[5].

Paracoccidioidomycosis may affect the adrenal glands and is one of the most common causes of primary adrenal insufficiency (Addison's disease), usually asymptomatic and causing an overall increase of the gland due to caseous necrosis[5].

All segments of the digestive tract can present lesions, from the mouth to the anus; however, the lesions are more common in organs containing more lymphoid tissue, such as the appendix, the terminal ileum, and the right colon. Stenoses, slow transit, ulcerations, fistulas, and perforations have been found[5]. The patient in our case presented a large amount of bloody nasogastric aspirate.

Bone disease occurs in 20% of cases and most frequently involves the clavicle, ribs, acromion, and radius. It is usually asymptomatic, osteolytic, and asymmetrical[5]. In the present case, the patient presented rounded osteolytic images inside the humeri, sternum, and ilium wings, leading to a hypothesis of multiple myeloma.

P. brasiliensis is sensitive to most antifungals. Itraconazole has been reported as the most effective therapeutic option in a shorter period of time in the literature. However, considering that itraconazole is not available in most of Brazil, the sulfamethoxazole-trimethoprim combination is the most often used alternative for outpatient treatment of paracoccidioidomycosis. In the severe forms, requiring hospitalization, patients should receive amphotericin B or sulfamethoxazole/trimethoprim intravenously. The duration of treatment is related to the severity of the illness and the medication used. It is a long-term treatment that facilitates the control of the clinical manifestations of the mycosis and prevents relapses[4]. In the present case, following the guidance from the HAIC team, we chose to add sulfamethoxazole/trimethoprim to the treatment.

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