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Emergence of acute/subacute infant-juvenile paracoccidioidomycosis in Northeast Argentina: Effect of climatic and anthropogenic changes?

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Abstract

Argentina has two endemic areas of paracoccidioidomycosis (PCM). Bordering Paraguay and Brazil, Northeast Argentina (NEA) comprises the area with the highest incidence where the chronic adult clinical form has historically been reported. Juvenile form in children and adolescents is rare in this area since only one case was reported in the last 10 years. Despite this, between 2010 and 2012, several cases of acute/subacute clinical forms in children aged 10 to 16 (median 12) were detected. In the last decade, the NEA region has been exposed to ecological variations as consequences of certain climatic and anthropogenic changes, including El Niño–Southern Oscillation phenomenon during 2009, and deforestation. The region has also suffered from the significant ecological effects of the construction of one of the biggest hydroelectric dams of South America. This study aims to describe clinical and epidemiological aspects of acute/subacute PCM cases detected in children from NEA and to discuss climatic and anthropogenic changes as possible contributing factors in the emergence of this disease in children. This acute/subacute PCM cluster was characterized by severe disseminated and aggressive presentations to localized form, with a high spectrum of clinical manifestations uncommonly observed. Due to the lack of experience in acute/subacute PCM in children in the studied area and the atypical clinical manifestations observed, the diagnosis was delayed. In order to avoid misdiagnosis, a higher level of suspicion is now required in NEA and countries bordering the southern part of the endemic area, which are affected by the changes discussed in this article.

Key words: Paracoccidioidomycosis, infant/juvenile, ecological influences, Argentina.

Introduction

Paracoccidioidomycosis (PCM) is a systemic fungal infection endemic in Latin America and most frequently reported in Brazil, Venezuela, Colombia and Argentina. It is caused by thermally dimorphic fungi nested within the genus *Paracoccidioides*.[1–6]

Recently, molecular tools allowed to revise the taxonomy of this genus determining two species, *P. brasiliensis* and *P. lutzii*. Moreover, genetic analysis revealed that *P. brasiliensis* is not a single species but rather a species complex comprising at least four genetic entities: S1, PS2, PS3, and PS4. However, the clinical impact of this genotypic diversity, if any, has not yet been investigated.[7–9]

The infection is usually acquired in the first two decades of life, and it is commonly subclinical, although the fungus can also cause chronic and severe diseases.[6,9,10] It is estimated that 10 million people are infected with *Paracoccidioides* spp. in Latin America, of whom only about 1–2% will develop PCM.[6] In Northeast Argentina (NEA), an infection rate of adults ranging 10.9%–20% is estimated. In contrast, only 1.6% of the child population, aged from 2 to 14 years with an average of 10 years, has had previous contact with *P. brasiliensis*.[11,12]

PCM predominantly afflicts adult males engaged in agriculture and it has a peculiar gender distribution with a preference for adult males at a ratio of ≥11 to 1. The disease has mostly a chronic profile and acute/subacute forms accounting for less than 15% of all reports.[3,8] Even more, PCM is uncommon in children and adolescents. In this population, the acute/subacute clinical form[13] was described and represents only 3–5% of all cases reported.[4,14,15] Despite the low incidence, it is a severe clinical condition, potentially life-threatening and mortality rates may be high.[6,15]

Certain environmental and ecological factors have been associated with a high PCM prevalence, including moderate-to-high annual precipitation rates, tropical and subtropical forests, waterways and certain types of soils.[3,6,16] Barrozo et al. described a cluster of acute/subacute PCM cases and its relationship with the weather variability as a significant factor.[17,18] These authors suggested that absolute air humidity, soil water storage, and Southern Oscillation Index have enhanced human infection.[3,6,17] El Niño Southern Oscillation (ENSO) is a fluctuation of the ocean–atmosphere system that originates in the tropical Pacific and is one of the most important sources of annual global climate variability. ENSO most intensely affects the tropics. In Southeastern South America, El Niño and its counterpart La Niña are associated with characteristic patterns of rainfall and temperature, which can include extreme events such as heavy rainfall and flooding. By altering climate conditions, ENSO can have severe effects on key health determinants.[19,20]

During 2009, the ENSO phenomenon affected the NEA area with rains above normal rates.[21] In addition to this important climatic influence registered, anthropogenic changes with ecological variation were introduced in NEA in the last decades. This region has been exposed to ecological variations as consequences of deforestation, changes in agriculture practice and the effects of the construction and operation of Yacyretá, one of the biggest hydroelectric dams of South America.[12,22]

Argentina has two well-defined PCM endemic areas; one is located in the Northwest of the country (NOA), including only the subtropical part of Salta and Jujuy provinces. The more extensive area with the highest PCM incidence is located in NEA, bordering Paraguay and Brazil, including Corrientes, Chaco, Misiones, and the northern part of Santa Fé and Entre Ríos provinces (Fig. 1). In this area the chronic adult form has historically been diagnosed and scarce knowledge gained about the juvenile form in children and adolescents since only one case was reported in the last 10 years.[23–25] Despite this, between 2010 and 2012, several cases of acute/subacute clinical forms in children were detected in NEA.

This study aims to describe clinical and epidemiological aspects of six cases of acute/subacute PCM detected in children from Northeast Argentina and to discuss their relationship with the climatic and anthropogenic changes that occurred in this area as possible contributing factors of the emergence of this disease in children.

Methods

This retrospective cohort study was conducted from 2010 to 2012 including six acute/subacute juvenile PCM cases admitted to the pediatric infectology sector of Hospital Pediátrico Dr. Avelino Castelán, Resistencia city (27°27′29″S, 58°58′31″W), and Hospital Pediátrico Juan Pablo II, located in Corrientes city (27°28′46″S 58°50′20″O), both from NEA.

Inclusion criteria were native patients with a definitive diagnosis of PCM by identification of *Paracoccidioides* sp. through histopathology and mycological analysis of clinical specimens and classification of the acute/subacute form by clinical findings based on a consensus in PCM.[13] Medical records of these patients were collected, and information concerning epidemiological, clinical, and therapeutic data was documented.

The therapeutic choice was based on the clinical presentation and the availability of drugs within the public

Figure 1. Endemic areas of paracoccidioidomycosis in Argentina. 1–6: Location of residence of the six cases detected in Northeast Argentina. This Figure is reproduced in color in the online version of *Medical Mycology*.

health service. Doses of amphotericin B 1 mg/kg/day and itraconazole 10 mg/kg/day were used. When the clinical improvement allowed leaving the intravenous medication to continue on oral antifungal therapy, amphotericin B treatment was moved to itraconazole.

Double immunodiffusion (ID) reactions using *Paracoccidioides brasiliensis* B339 were applied as serological tests in order to follow up the clinical outcome of the affected patients. Although clinical improvement was observed, patients were treated until serology turned negative. Serological tests are important in the diagnosis of PCM as well and to follow-up the treatment success.

Disseminated PCM was considered when more than one organ was affected by the fungus. Localized forms were diagnosed when a sole organ was involved.

Results

We present six PCM juvenile type cases detected in a short period of time in children from NEA. Median and the average age were 12 years (minimum 10, maximum 16).

Figure 1 shows the NEA region and locations where the patients live. Two patients, living in a strictly urban ambient, referred from Corrientes city, and four cases from different regions of Chaco province, two of them living in a rural ambient. No trips to other regions were reported before the onset of symptoms in all urban or peri-urban cases.

Demographic, clinical data and prognosis of the patients are summarized in Table 1.

The median time of symptoms' onset until PCM diagnosis was 2 months (minimum 1, maximum 4).

Proven PCM was obtained in 100% of cases by identification of *Paracoccidioides* sp. in clinical specimens. No coinfections were detected in any case.

The lymph nodes were the most affected organ (5/6), followed by bone, skin, spleen, and liver (3/6), and then lung in 2/6 of cases. Pericardial effusion and pulmonary involvement were observed in the most severe cases.

A 10 year-old patient (case 2) presented with exacerbated subcutaneous lumps in neck, scalp, left eyelid, and jaw zones, one of the most striking visual clinical manifestations observed in this group of cases. Figure 2 shows lumps in the left eyelid and maxillary right, and Figure 3 is the cranial X-ray of the same patient showing frontal and parietal osteolytic bone lesions. Biopsies of these abscesses showed abundant *Paracoccidioides* cells. Although skin lesions are reported as frequent in this clinical form,[14,36] only case 6 showed erythematous papules.

In four cases more than one organ was affected by the fungus, and only one localized form was detected in a 16 year-old patient. Figure 4 shows the osteolytic lesion in the leg diaphysis of this case, observed using X-ray and computed axial tomography (CAT).

Fever and emaciation as consequences of poor nutrition were observed in all disseminated PCM cases. Four of these

Table 1. Demographic, clinical approach, and prognosis of the 6 cases of acute/subacute infant-juvenile PCM presented in Northeast Argentina.

Location Province	Case 1 Saenz Peña Chaco	Case 2 AviaTerai Chaco	Case 3 Resistencia Chaco	Case 4 Las Breñas Chaco	Case 5 Corrientes city Corrientes	Case 6 Corrientes city Corrientes
Age/Sex	10 years/Female	10 years/Male	12 years/Male	13 years/Male	16 years/Female	13 years/Male
Area	Periurban	Rural	Urban	Rural	Urban	Urban
Progress	4 months	2 months	1 month	2 months	1 month	2 months
Clinical profile	Severe malnutrition Fever Asthenia Adenomegaly Hepatosplenomegaly Abscessed and fistulized subcutaneous lymphnodes Osteolytic lesions in long and cranial bones with pathologic humerus fracture Pericardial effusion	Emaciation Fever Asthenia Hepatosplenomegaly Lumps in neck, scalp, left eyelid and maxillary right (Fig. 2) Clusters of lymphonodes in neck, thorax, abdominal cavity and retroperitoneum. Parietal, frontal and orbital osteolytic bone lesions (Fig. 3) Right lung nodule	Emaciation Fever Asthenia Submandibular lymph nodes Mediastinal adenomegaly Pulmonary nodules	Emaciation Fever Asthenia Hepatosplenomegaly Cervical adenomegaly Abdominal ganglionar hypertrophy Acute abdomen Pericardial effusion	Pain and swelling in ankle and right leg Osteolytic lesion only in the diaphysis of right leg (Fig. 4)	Fever Erythematous papules in limbs and trunk Fauces ulcers and oropharyngeal nodules Supraclavicular and cervical lateral lymphadenopathy Retroperitoneal adenomegaly
Serology (ID)	1/8	1/8	1/8	No reactive	N/D	1/32
Treatment	AMB/Itraconazole	AMB/Itraconazole	Itraconazole	AMB/Itraconazole	Itraconazole	AMB/Itraconazole
Response/Evolution	Died	Good	Good	Good	Good	Good

AMB, Amfotericin B; ID, Doble immnodiffusion serology test using Pb B339; N/D, Not done.

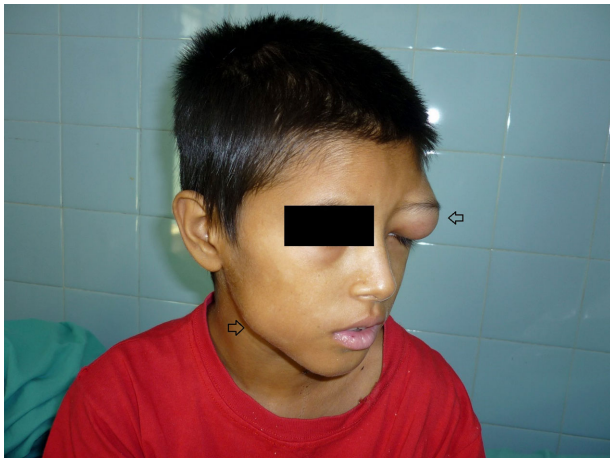

Figure 2. Disseminated paracoccidioidomicosis, case 2. Subcutaneous lumps in left eyelid and maxillary right in a 10 year-old patient (indicated by arrows). This Figure is reproduced in color in the online version of *Medical Mycology*.

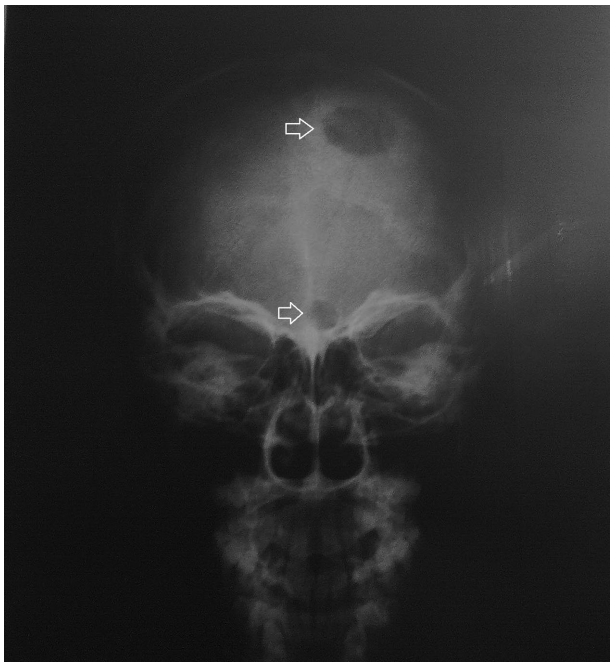

Figure 3. Disseminated paracoccidioidomicosis, case 2. Cranial X-ray showing frontal and parietal osteolytic bone lesions (arrows).

cases were accompanied by asthenia. Hospitalization was necessary to promote intensive healthcare support and/or intravenous therapy with amphotericin B. These clinical manifestations were not observed in the patient with the localized form, the only patient who did not require hospitalization.

Amphotericin B was used in severe cases (4/6) until clinical improvement allowed the use of itraconazole. The good improvement was obtained with oral itraconazole in mild to moderate cases; indeed, a rapid response showed case 5, with the localized form.

Five patients completed treatment and progressed to clinical cure; there was one death due to multi-organic impairment and extreme emaciation.

Serological cure was obtained in 4/6 of cases. ID test was not reactive in one disseminated case and was not performed in the patient with the localized form.

Discussion

Since a single case was reported in the last 10 years, the incidence of the juvenile type form of PCM in children from the NEA area is almost unknown, although, these detected cases suggest a new trend in PCM.[25] This is an interesting fact, taking into account that children and young people aged 3–13 years have a restricted migratory profile and are therefore considered valuable epidemiological markers. The places where they live may furnish valuable data concerning changes in the PCM epidemiology as well regarding the natural habitat of *Paracoccidioides*.[4,17,26]

Interestingly, most of the patients reported in this study lived in strictly urban areas without any known exposure to the rural environment or any recognized risk factor associated with PCM. Although PCM is endemic in populations that live in rural areas, changes in the demographic and geographic patterns of the population with PCM have been observed in the last few years, with the occurrence of PCM in urban areas.[15,27] Juvenile PCM in urban areas was previously reported by other authors.[28,29]

The juvenile type systemic disease of PCM may progress from the primary focus of infection without a latency period. Once the disease is established, the patient may develop an acute or subacute pattern of clinical manifestations and a fast clinical deterioration.[14,28,30,31] Disseminated PCM presentations reported in this article were severe. In a few months or weeks, an acute and febrile rapid course with weight loss and multi-organic affectation was observed.

As a consequence of the tropism of *Paracoccidioides* to the monocyte-phagocyte system, a marked involvement of the reticuloendothelial system characterized this clinical form.[31–34] Similar to other reports in children and adolescents,[15,28,32,35–37] the main clinical manifestation in our patients with disseminated forms were fever with lymphatic involvement.

Poor nutrition may compromise cellular immunity and has been considered an important predisposing condition to developing PCM, especially in younger adults with extensive abdominal lymphadenopathy.[3,35,36] This situation was also observed in our disseminated cases. The aggressiveness and high mortality rate reported for this clinical form are enhanced by severe malnutrition[14,30,31,36] as was

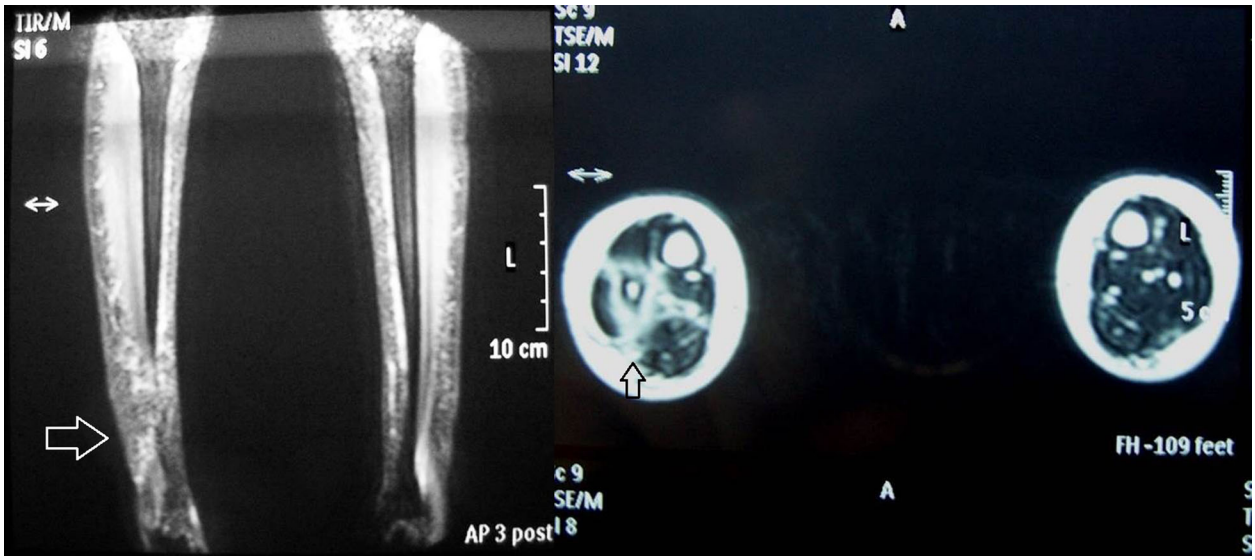

Figure 4. Localized paracoccidioidomicosis, case 5. Osteolytic lesion in the leg diaphysis (arrows) observed using X-ray (left image) and computed axial tomography (CAT, right image). This Figure is reproduced in color in the online version of *Medical Mycology*.

observed in case 1. The rapid evolution led to the death of the patient, showing the extreme emaciation with the most diverse clinical manifestations described in Table 1, like other malnourished PCM cases previously reported.[15,17] In addition, as was reported in cases of severe acute PCM in children,[32] case 4 presented pericardial effusions.

Bone involvement in lytic lesions is frequent in this clinical form, particularly in children.[17,32,35,36] Multiple osteolytic extensive lesions were present in three cases. It is important to highlight case 5, in which the localized pain and swelling because of the osteolytic lesion in the right leg diaphysis was the only one clinical manifestation, being the only case of localized PCM of patients reported in this article. Although similar localized cases were reported by other authors, [35] this single case was detected in a 16 year-old girl. The effect of 17-beta-estradiol protecting women from developing the disease but not the infection is well known.[38] Probably, this hormonal influence played a protective role in this case, explaining the disease less severe than that observed in other prepubescent individuals.

In contrast to the chronic form, pulmonary lesions in the acute/subacute form are very unusual as a clinical pattern.[14,30,31] Radiological evidence of pulmonary involvement was observed in cases 2 and 3, both presenting lung nodules.

In contrast to the predominance of PCM in adult male as described, no difference between genders is reported in prepubescent individuals who present the acute/subacute or juvenile clinical form.[3,38] According to those reports, not a high male to female ratio was observed in the few cases presented in this study.

The occurrence of childhood PCM indicates early exposure to the fungus. Disturbance of the PCM reservarea, specially the soil disturbances in sylvan forests, is conducive to paracoccidioidal infection.[4] Climatic influences on PCM were reported by establishing ecologic variables correlated to the distribution of this infection and the increasing of the incidence of disseminated forms in children, between 3 and 13 years old, among who PCM had been infrequent.[3,16,37] The effect of absolute air humidity, soil water storage, and ENSO in the incidence of PCM cases was already reported, and it was suggested that such variables influence the conditions favoring infection of humans.[18] The enhanced human infection by the ENSO effect and a records of 91 acute/subacute patients in whom infection was calculated to have occurred 1–2 years previously were discussed.[17] Even more, a cluster of juvenile acute/subacute form potentially correlated to the 1982–83 ENSO climatic anomalies was reported.[18] A similar situation has occurred in NEA. Based on the ONI index[22] during 2009–2010, moderate ENSO occurs in South America including the NEA area. Interestingly, cases presented in this study occurred during 2010–2012, which may be a consequence of the ecological effects generated by this climate phenomenon. After the period of time in which these six cases appeared, no new cases have been notified in the NEA area up to May 2017 and no strong or moderate ENSO events occurred since 2012.

Previous studies in the NEA area have also suggested that anthropogenic changes have a direct influence on the rate of human infection with *Paracoccidioides*.[12] Since the 1990s, the areas where the patients were diagnosed with PCM in this study have suffered deforestation and a strong impulse

to change their type of crop and agricultural practices, with soy bean replacing cotton.[39,40] In addition, during the last decades, the NEA region has been exposed to the consequences of the construction and operation of Yacyretá, one of the biggest hydroelectric dams in South America.[12,41] Major works involve a permanent environmental impact and the impact of a hydroelectric plant and its artificial lake has been associated with the increased number of PCM cases and infection rates in Brazil.[42,43]

In order to emphasize this discussion about the relationship of this PCM outbreak with climatic and anthropogenic changes, there was no increase in cases reported in the endemic area located in NOA within the same period. This zone was not affected by ENSO or by anthropogenic changes in the last decade, as recorded in NEA.

Serological tests are important in the diagnosis of PCM and to follow up the treatment success. ID reaction using Pb B339 has 80% of sensibility and more than 90% of specificity.[13] No reactive test was obtained in one case of all proven PCMs presented. This result highlights the importance of considering the geographical origin of the PCM cases and exploring specifically the circulating *Paracoccidioides* species in the NEA area. An explanation may be that serum antibodies from PCM patients from different regions are unable to precipitate antigens from the reference antigen strain Pb B339. Therefore, differences in the antigenic composition, probably related to phylogenetic peculiarities in *Paracoccidioides* species circulating in this area, might be considered in the diagnosis of PCM in Argentina.[15,44,45]

Endemic mycoses are a frequent health problem in Latin American countries, with a significant impact on public health, therefore, an early and precise diagnosis and appropriate treatment remain important.[6] Due to the lack of experience in acute/subacute PCM and the atypical clinical manifestations in children in the studied area, the diagnosis was a challenge and it was delayed. Consequently, when patients were diagnosed, many were already severely ill with multiple organs compromised by the disease.

This study provides evidence about the emergence of cases of acute/subacute PCM in the infant population from the NEA area, during 2010–2012. This emergence was characterized from severe disseminated and aggressive presentations to localized form, with a high spectrum of clinical manifestations uncommonly observed in this area. The likely direct connection with ecological variations as a result of climatic and anthropogenic changes in the area was discussed. In order to avoid misdiagnosis, a higher level of suspicion is now required not only in NEA but also in bordering countries included in the southern part of the South American endemic area which are affected by the changes herein discussed.

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Declaration of interest

The authors declare no conflict of interest.

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