PARACOCCIDIOIDOMYCOSIS AND AIDS: REPORT OF THE FIRST TWO COLOMBIAN CASES

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SUMMARY

The records of the first two Colombian patients with AIDS and paracoccidioidomycosis are presented. Both patients were males and had no known risk factors for HIV although in the past they had worked in the field where they could have been infected with the fungus. They exhibited the juvenile type of disease with multiple organ system involvement and symptoms of short duration. They were deeply immunodepressed as indicated by less than 100 CD4 T lymphocytes per mL; however, serologic tests revealed circulating anti-*Paracoccidioides brasiliensis* antibodies and in one patient the first diagnostic clue came from such tests. In one case, the mycosis preceded the AIDS diagnosis while in the other, both pathologies were discovered simultaneously. Antimycotic therapy with itraconazole was administered for over 10 months, with an initial dose of 200 mg/day followed by 100 mg/day; marked improvement of the mycotic signs and symptoms was soon noticed an there have been no signs of relapse. The patients' improvement was also due to the combined retroviral treatment that was instituted. In spite of the rarity of the AIDS-paracoccidioidomycosis association, physicians practicing in endemic areas should consider the presence of the mycosis in immunosuppressed patients, since a prompt diagnosis and institution of combined antimycotic-anti-retroviral treatments would result in patient improvement and survival. It appears possible that the longer survival time of today's AIDS patients would give the quiescent fungus the opportunity to revive, multiply and cause overt disease.

KEYWORDS: Paracoccidioidomycosis; AIDS; Diagnosis, Antimycotic treatment.

INTRODUCTION

The endemic area for paracoccidioidomycosis comprises almost all of the South American countries as well as most of those in Central America^{9,10,16,18,26}. The disorder has also been reported in nonendemic areas but always in patients who had visited or lived in Latin America^{9,19}. In Brazil, the disease is an important health problem and the number of cases exceeds 6,000^{16,18}. In countries like Colombia this disorder, although not as frequent, is also of importance^{9,10}.

The AIDS pandemia has affected all the countries within the confines of the paracoccidioidomycosis endemic area; it is estimated that the number of HIV-infected individuals in Latin America is as large as the number of infected individuals in the United States^{5,8,24}. It is well-known that the course of this viral infection is characterized by the occurrence of intercurrent opportunistic infections which define the progression from HIV infection to overt AIDS^{12,23,24}. Among such infections, certain systemic mycoses, mainly cryptococcosis and histoplasmosis, are responsible not only for an important number of deaths but also for a high morbidity rate^{5,12,22,23,24}.

AIDS-associated cryptococcosis is frequent in Brazil³⁸, Argentina⁴ and Colombia^{1,2,30,35}. *Cryptococcus neoformans* var. *neoformans* is isolated from approximately 6-10% of the HIV-infected individuals in these countries. Similarly, *Histoplasma capsulatum* var. *capsulatum* causes disseminated disease in at least 4-6% of the AIDS population in Latin America^{1,2,31,34,35,37}. In contrast to the frequency of these two mycoses in HIV-positive patients, the number of paracoccidioidomycosis patients in the same group is notorioulsy low^{14,20,21}.

The first five cases of paracoccidioidomycosis and AIDS were reported simultaneously in 1989^{3,7,13,33} and by 1994-1995 this figure had risen to 31 cases^{14,15,17,20,21}. With the exception of a patient from Venezuela⁷, the remaining cases have been all from Brazil. In 1995, the estimated incidence of the HIV- paracoccidioidomycosis association in the latter country was 0.09%²⁰. More recently, a series of 13 additional cases have been reported^{11,27,28,29,36}.

During the period from 1989 to 1998 the Mycology Unit of the Corporación para Investigaciones Biológicas and the Laboratorio

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de Salud Pública diagnosed 68 cases of cryptococcosis and 67 of histoplasmosis in HIV-positive patients. Nonetheless, among 76 patients with paracoccidioidomycosis diagnosed during the same period at both Institutions, only 2 occurred in HIV-infected individuals, who are the cases described in this report.

CASE REPORTS

CASE 1: In January 1995, a 26 year old heterosexual male, the administrator of a rural hotel who had been a farmer a decade earlier, sought medical care due to symptoms of 4 months duration consisting of dry cough, fever, abdominal cramps and weight loss (8 kg). Physical examination also revealed the presence of hypertrophied cervical, inguinal and axillary lymph nodes, as well as finger onychomycosis. With the presumptive diagnosis of lymphoma or tuberculosis, a lymph node was resected for histopathologic study which revealed lymphoreticular hyperplasia with no malignancy; acid-fast bacilli were not found. A chest X ray was normal. Once the above two diseases were ruled out, the patient was referred to our laboratory for fungal studies which revealed reactive serologic tests for P. brasiliensis, with a precipitin band in the agar immunodiffusion and titers over 1:1,024 in the complement fixation (CF) test. A sputum sample showed P. brasiliensis yeast cells and later on the fungus was isolated in culture.

The diagnosis of paracoccidioidomycosis was then established. However, due to the patient's marked weight loss and the presence of the juvenile form of the mycosis, HIV tests were ordered and found to be positive. At the time of diagnosis of both diseases there were 94 CD4 T lymphocytes per mL, with a CD4/CD8 ratio of 0.07. Treatment for the mycosis was then begun with itraconazole at a dose of 200 mg/day for a period of 12 months. The clinical response was satisfactory since fever disappeared, lymph node hypertrophy diminished and the patient gained 7 kg. The itraconazole dose was then reduced (100 mg/day) and at present, the patient has been taking this dose for 13 consecutive months, with no relapse. Thus, treatment has lasted for 25 months and will

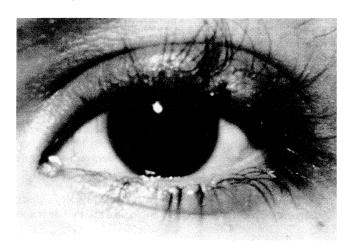


Fig. 1 - Isolated skin lesion in a patient (case N° 2) with paracoccidioidomycosis and AIDS. The eyelid shows an infiltrated plaque on the palpebral border accompanied by inflammation.

be permanent. Combined anti-retroviral therapy with lamivudine, AZT and indinavir was also given 7 months after AIDS diagnosis when this type of therapy became available in Colombia.

CASE 2: A heterosexual 30 year old male, a farm watchman and a farmer 15 years previously, seeked medical help in April 1997 due to the presence of an ulcerated lesion in the eyelid that had been present for the last 3 months and had enlarged since then. Other symptoms reported were dry cough, a 5 kg weight loss, malaise, and enlargement of cervical lymph nodes. Upon clinical examination, an isolated ulcerated lesion on the free border of the left upper eyelid was found (Fig. 1); there were hypertrophied cervical, axillary and inguinal lymph nodes as well as mucosal candidiasis. Tests for HIV infection ordered at that time were positive; CD4 T lymphocytes

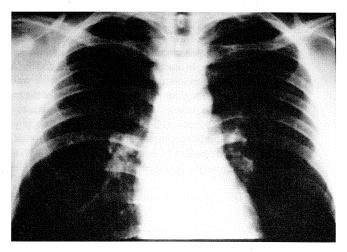


Fig. 2a - Chest X-ray of a patient (case N° 2) with paracoccidioidomycosis and AIDS. Hypertrophied hilar lymph nodes but no parenchymal lesions

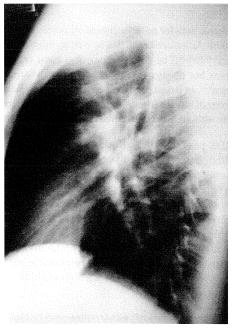


Fig. 2b - Chest X-ray of a patient (case N° 2) with paracoccidioidomycosis and AIDS. Lateral view showing the above alterations in detail.

were 72 per mL, with a CD4/CD8 ratio of 0.08. A chest X ray revealed the presence of enlarged hilar nodes but no parenchymal alterations (Fig 2).

Direct KOH examinations of the exudate obtained from the palpebral ulceration as well from sputum samples revealed multiple budding *P. brasiliensis* yeast cells; the fungus was later isolated in culture. Serological tests with the homologous antigen showed precipitin band 1 in the immunodiffusion test and a CF titer above 1: 1,024.

Treatment with itraconazole at a dose of 200 mg/day was started and given for 3 months; after this time, the dose was reduced to 100 mg/day due to elevation of the liver function tests. At the time of this report, treatment at this dose has been given uninterruptedly for 10 months and the response has been adequate since the tegumentary lesion and the fever disappeared after 3 months of therapy and the enlarged lymph nodes diminished in size. Antiretroviral therapy with lamivudine, AZT and indinavir was started 6 months after initiation of the antimycotic therapy.

The laboratory data obtained before and during treatment for both patients, indicated that there was a trend towards increasing hemoglobin concentration and leukocyte counts. Alkaline phosphatase levels were elevated from the beginning in both patients but in patient 1, they became normal after 12 months of therapy. The remaining liver function parameters were within normal values in one patient but in the other, they increased after 3 months of itraconazole therapy. In both patients, itraconazole levels were measured every 2 months and found to be over 1 $\mu g/mL$ after one month in patient 2 and after 3 months in patient 1. They continued to be above 3.0 $\mu g/mL$ for the following 8 months of therapy in patient 1 and were somewhat lower in patient 2. Serologic follow-up revealed decreasing CF titers in both patients as well as disappearence of the precipitin band during therapy (Table 1).

TABLE 1
Serologic evaluation of two AIDS patients with paracoccidioidomycosis

Complement fixation	Complement fixation titers Patients:				
	1	2			
Diagnosis	> 1:1024	> 1:1024			
During therapy at:	-				
3 months	1:512	1:32			
6 months	1:128	1:128			
9 months	1:16	1:32			
12 months	1:8	ND *			
18 months	Non reactive	ND *			
25 months	Non reactive	ND *			

^{*} ND = no data

DISCUSSION

Paracoccidioidomycosis has been rarely reported in patients infected with the human immunodeficiency virus, as demonstrated by the fact that in the 10 years elapsed after the diagnosis of the first cases with this association, less than 50 patients have been reported in the literature^{3,6,7,11,13,14,15,17,20,21,27,28,33,36}. Under-reporting is probably common but nonetheless this is in sharp contrast with the occurrence in the same geographical areas of cryptococcosis and histoplasmosis, diseases that are frequent in HIV-infected individuals^{1,2,4,24,30,31,34,35,37,38}. Of note, *P. brasiliensis* is also rarely observed in iatrogenically immunosuppressed patients as well as in those with cancer ²⁰.

The patients reported here shared several interesting characteristics, not to mention the fact that they are the first to be reported in Colombia, a country where paracoccidioidomycosis is frequently diagnosed^{9,10}. They had no record of predisposing factors for HIV, such as homosexuality or drug addiction but their past agriculture-related occupation represents the most probable source of infection with *P. brasiliensis*, even if the patients were no longer working in the field, since prolonged latency is common in this mycosis, as demonstrated by the cases diagnosed outside endemic areas^{9,16,18,19,26}.

Both patients were severely immunosuppressed at the time of diagnosis and had less than 100 CD4 T lymphocytes/mL, indicating that the viral process was well advanced, as also observed by other authors^{6,11,15}. Nonetheless, infection with HIV had not been previoulsy considered. One of the patients was, in fact, suspected to harbor the virus after the diagnosis of the mycosis had been established. The presence of oral candidiasis at the time of consultation for the skin lesion led the attending physician to consider AIDS in the second case. These observations indicate that paracoccidioidomycosis can either predict the viral infection or accompany other more frequent heralding infections^{14,20,21} such as mucosal candidiasis^{5,18,19}.

Consequently, physicians working in endemic areas for paracoccidioidomycosis should be aware of its presence in immunosuppressed patients, even if this type of association is infrequent, since a prompt diagnosis allows the institution of specific therapy, which results in the improvement of patient health²⁵.

Our patients presented the subacute juvenile form of paracoccidioidomycosis with symptoms of short duration (3-4 months) and had multisystemic organ involvement, including the lungs and various lymph node chains. These observations are common to several of the AIDS-paracoccidioidomycosis patients previoulsy reported^{3,8,11,13,14,17,20,27,28,29,33}. Although radiologic chest alterations were noticed only in one of the patients, *P. brasiliensis* was isolated from pulmonary secretions in both of them. This has also been reported for other AIDS cases^{14,17,20}. However, lung involvement is rarely reported in juvenile cases probably because of the more severe manifestations observed in other organs^{9,16,18}.

In spite of the marked immunosuppression recorded in both cases, anti-*P. brasiliensis* antibodies were readily detected serologically. In one patient the mycotic nature of the process was confirmed by high CF titers. According to the literature, the presence of homologous antibodies has been recorded in only half of the patients tested^{14,20,28,29}. However, a search for diagnostic clues by immunological methods should always be undertaken since their value goes beyond the mere diagnosis, permitting periodical monitoring of course of the disease^{14,18,20,26}.

In contrast with the high morbidity rate (close to 30%) described previously for patients treated with antimycotics^{14,20,28}, the two patients reported here who received itraconazole have had prolonged survival (31 and 14 months after diagnosis of AIDS) and have experienced less morbidity. Determination of the plasma azole levels allowed a more rational control of drug absorption, since a number of AIDS patients have hypochlorydria which prevents reaching the required drug concentration. Furthermore, we believe that the simultaneous administration of the three anti-retroviral agents, even if given later in the course of the viral infection, had an important effect on the patients' survival since such therapy allows to control viral multiplication, thus preventing further health deterioration³².

The scarcity of AIDS patients that develop paracoccidioidomycosis, approximately 50 in the Latin American endemic area, continues to be puzzling, especially when this figure is compared with the numerous cases of cryptococcosis and histoplasmosis known to occur in the region^{1,2,4,24,30,31,34,35,37,38}. It is possible that, as demonstrated by the last 13 patients recently presented at a Brazilian Congress^{28,29,36} or published elsewhere^{11,17,21,27}, and also by the two cases reported here, the association of the two diseases may become more frequent in the future. It appears possible that the longer survival time obsserved in the present AIDS patients would give the quiescent fungus the opportunity to revive, multiply and cause overt disease in a larger number of cases.

RESUMO

Paracoccidioidomicose e AIDS: relato dos dois primeiros casos colombianos.

Relato dos dois primeiros casos de pacientes colombianos com AIDS e paracoccidioidomicose. Os pacientes, ambos masculinos, não tinham conhecimento do fator de risco por HIV, embora tivessem no passado trabalhado no campo onde poderíam ter sido infectados por fungos. Eles tiveram o tipo juvenil da doença em vários orgãos com sintomas de curta duração. Eles estavam profundamente imunodeprimidos, com menos de 100 CD4 T linfócitos por mL; todavia, os testes sorológicos revelaram anticorpos circulantes anti-*Paracoccidioides brasiliensis* em um dos pacientes e os primeiros indícios diagnósticos vieram destes testes. Em um caso, a micose precedeu o diagnóstico da AIDS enquanto que no outro, ambas patologias foram descobertas simultaneamente. A terapia antimicótica com itraconazole, foi dada por 10 meses, começando com 200mg/dia e seguida por 100 mg/

dia: foi notada pronunciada melhora nos sintomas e sinais da micose, sem recorrência. A melhora dos pacientes provavelmente também foi devido à combinação do tratamento retro-viral que foi ministrado. Embora rara a associação de AIDS com paracoccidioidomicose, médicos que atuam em áreas endêmicas devem considerar a presença de micoses em pacientes imunodeprimidos como diagnóstico imediato e instaurar o tratamento combinado antimicótico/antiretroviral, que resultaria em melhora e sobrevivência dos pacientes. Parece que é possível que o tempo de sobrevida longo visto nestes pacientes com AIDS dará tempo para o fungo quiescente ressurgir, multiplicar e produzir a doença de forma expressiva.

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