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PARACOCCIDIOIDOMYCOSIS ASSOCIATED WITH ACQUIRED IMMUNODEFICIENCY SYNDROME. REPORT OF SEVEN CASES

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SUMMARY

We report the clinical findings and evolution of seven patients (five men and two women), the majority of them intravenous drug users, with paracoccidioidomycosis associated to acquired immunodeficiency syndrome (AIDS).

In four of the patients the paracoccidioidomycosis was restricted to the lung and in the three others was generalized with cutaneous involvement. Only two of them had lived recently in rural area, an indication of the possible reactivation of latent focal infection in the other five patients.

The recognition of the role of cell-mediated immunity in host defense against *Paracoccidioides brasiliensis* leds to the prediction of a growing occurrence of the paracoccidioidomycosis-AIDS association in areas that are endemic for these diseases.

KEYWORDS: . AIDS; Epidemiology; *P. brasiliensis*; Paracoccidioidomycosis.

INTRODUCTION

Paracoccidioidomycosis is a deep mycoses endemic in several countries in Latin America, especially in Brazil [10]. As occurs with other deep mycoses, patients are infected by inhaling mycelia or conidia of *Paracoccidioides brasiliensis*, with the instalation of a primary pulmonary complex [8, 16]. In most persons, the natural defense mechanisms can either eliminate the agent or establish an equilibrium between host and agent. In the latter case, the fungi would continue to be viable in the form of latent foci of infection [6]. In a minority, however, the disease progress from this primary pulmonary focus.

Since cell-mediated immunity is the basic defense mechanism against *P. brasiliensis* [13, 14], a dysfunction of this system induced by immunosuppressive factors such as chemotherapy, corticotherapy or infection with human immunodeficiency virus (HIV) may result in paracoccidioidomycosis-diseases from the reactivation of the quiescent foci [11, 17-20]. In Brazil, the association between paracoccidioidomycosis and acquired immunodeficiency syndrome (AIDS) is particularly important [2-4, 9, 15] because of the progressive dissemination of HIV to small and medium urban centers, especially in the Center-South region of the country [5], an area of high prevalence of infection with *P. brasiliensis* [1, 12]. In order to emphasize the growing occurrence of this association, we report 7 cases diagnosed at three different hospitals in the state of São Paulo.

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CASE REPORTS

Case 1

A 19-year old female using intravenous drugs, heterosexually involved with multiple partners and with positive anti-HIV serology detected by ELISA, sought the University Hospital of the Faculty of Medicine of Marilia (UH-FMM) with a pulmonary complaint characterized by coughing and bronchial secretion. Radiologic investigation revealed a diffuse reticular interstitial pulmonary infiltrate and examination of sputum permitted the identification of *P. brasiliensis*. There was no evidence of infection of other organs or systems.

Treatment with cotrimoxazole was started, with satisfactory results. During follow-up, the patient showed marked weight loss, diarrhea caused by *Isospora belli*, chronic genital mucocutaneous herpes simplex, oral candidiasis, and died 5 months afterwards.

Case 2

A 46-year old female patient using intravenous drugs, heterosexually involved with multiple partners and with positive anti-HIV serology detected by ELISA, sought the UH-FMM with pulmonary complaints. A chest X-ray showed an interstitial infiltrate in the base of the right lung. Examination of sputum revealed the presence of *P. brasiliensis*. Treatment with cotrimoxazole led to clinical improvement. During follow-up, the patient presented oral candidiasis, enterorrhagia and encephalitis of indeterminate etiology and died 2 months after the diagnosis of paracoccidioidomycosis.

Case 3

A 28-year old male patient sought the UH-FMM with countless ulcerated skin lesions, cervical, axillary and inguinal adenomegaly and intense weight loss (Fig. 1). A diagnosis of paracoccidioidomycosis was confirmed by the detection of *P. brasiliensis* in histopathological examination of a skin biopsy. There was no apparent involvement of oral mucosa or lungs.

In view of the sexual behavior of the patient and of the clinical characteristics of paracoccidioidomycosis, anti-HIV serology was investigated and found to be positive (ELISA).

The patient was treated with amphotericin B (acumulative dose of 2000 mg), with full regression of signs and symptoms. However, after 5 months, the clinical picture deteriored by presumable toxoplasmosis of the central nervous system, diagnosed by tomography and the patient died of *S. aureus*-induced septicemia. At this time the paracoccidioidomycosis appeared to be clinically inactive.

Fig. 1 - Case number 3 with multiples necrotic ulcers located on the face.

Case 4

A 31-year old male patient, heterosexually involved with multiple partners, was seen at the UH-FMM with pulmonary complaints. A chest X-ray revealed a macronodular infiltrate in the upper fields of both lungs. A presumptive diagnosis of tuberculosis was made, but examination of sputum revealed the presence of *P. brasiliensis*. There was no evidence of paracoccidioidomycosis in other organs. Serologic anti-HIV investigation was positive (ELISA) and complement-fixation and precipitation anti-*P. brasiliensis* reactions were negative. Treatment with cotrimoxazole was started but the patient did not return for follow-up.

Case 5

A 28-year old male from the rural area, a drug user heterosexually involved with multiple partners and with HIV-positive serology (ELISA), sought the

Regional Hospital of Sorocaba with pulmonary and constitutional complaints. Oral candidiasis and bilateral interstitial pneumonia suggestive of *Pneumocystis carinii* were diagnosed. Treatment with a combination of cotrimoxazole and ketoconazole was started with improvement. One month later he returned with skin lesions on the face, limbs and oral mucosa. Histopathological examination led to a diagnosis of paracoccidioidomycosis. He continued treatment with 400 mg/day ketoconazole with no resolution of the signs and symptoms, which was only obtained after the introduction of amphotericin B (cumulative dose of 1000 mg). The anti-*P. brasiliensis* serology performed before the amphotericin B was positive with a low titer in the complement-fixation reaction, and negative in the counterimmunoelectrophoresis reaction. Eight months after the diagnosis of paracoccidioidomycosis he developed an infectious pulmonary syndrome of indeterminate etiology and died.

Case 6

A 25-year old male from the rural area, a user of intravenous drugs heterosexually involved with multiple partners, sought the Regional Hospital of Sorocaba with a 3-month history of fever, diarrhea, weight loss and pulmonary complaints. His chest X-ray showed a diffuse interstitial and micronodular pulmonary infiltrate and he presented oral candidiasis and positive anti-HIV serology (ELISA). After one month of follow-up, *P. brasiliensis* was identified in sputum. Treatment with cotrimoxazole in combination with amphotericin B on the 12th day (cumulative dose of 837 mg) was instituted, with improvement. Three months later he developed signs and symptoms of meningoencephalitis due to *Cryptococcus neoformans* and a relapse of the pulmonary syndrome. He was treated with a total dose of 900 mg of amphotericin B, with clear clinical improvement. The patient suffered a relapse of neurologic and pulmonary symptoms 4 months later, when he was treated again with amphotericin B and cotrimoxazole, with improvement.

Case 7

A 42-year old male patient involved in homosexual practice was seen at the University Hospital of the Faculty of Medicine of Botucatu, with complaints of cervical adenomegaly of 3 months duration, ulcerated skin lesions and fever, with a recent 12 kg weight loss within this time. Examination revealed cervical, axillary and inguinal adenomegaly of up to 4 cm, with no inflammatory signs; multiple ulcerated skin lesions up to 3 cm located on the face, trunk and limbs; and hepatomegaly. Laboratory tests showed: positive anti-HIV tests (ELISA and Western blot); 5200 leucocytes; 1631 lymphocytes; Hb = 10.1 g%; Ht = 33.0%; CD4 = 67 cells/mm3, CD8 = 929 cells/mm3; and 3.7 g% hypergammaglobulinemia. Urea, creatinine, OGT, PGT, alkaline phosphatase, AgHbs, anti-Hbs, chest X ray, paracoccidioidin test, complement fixation reaction, precipitins, anti-*P. brasiliensis* immunodiffusion and immunofluorescence were normal or negative.

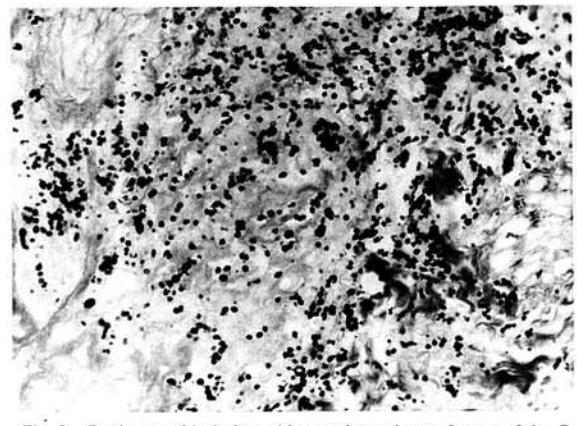

Fig. 2 - Section on skin lesion with countless minutes formes of the *P. brasiliensis*. with chains of elongated elements and multiple budding. Tissue section stained by the Grocott-Gomori method (x400).

The diagnosis was confirmed by the detection of minute *P. brasiliensis* forms upon histopathological examination of skin lesions (Fig. 2). A positive reaction against antigenic *P. brasiliensis* components with molecular weights of 71, 61, 51,43 and 27 kDa was detected by Western blot.

The patient was treated with 400 mg/day ketoconazole for 5 months and with cotrimoxazole after the 6th month, in combination with azidothymidine, with apparent clinical cure of paracoccidioidomycosis, weight gain, correction of anemia and stabilization of CD4 cells at about 55 cells/mm3. Fourteen months later, the patient presented a pulmonary infection of rapid course and died. Autopsy showed a generalized infection by *Cryptococcus neoformans*, with no evidence of residual *P. brasiliensis* infection.

DISCUSSION

Previous observation of paracoccidioidomycosis in patients under immunosuppressive treatment and the

awareness of the role of cell-mediate immunity in the mechanisms of host defense against *P. brasiliensis* permitted us to predict that HIV infection and the consequent occurrence of AIDS would cause a growing prevalence of the paracoccidioidomycosis-AIDS association in areas that are endemic for both diseases.

Although several laboratory tests, especially those related to immunologic profile and anti-*P. brasiliensis* serology, could not be obtained for the cases reported here, we believe that these reports are justified by the clinical characteristics and the course of the patients and by their epidemiologic importance. In this series (see table 1), mean patient age (29 years) was lower than that observed in isolated paracoccidioidomycosis and was consistent with that observed in AIDS, as also was the proportion of females. The predominance of use of intravenous drugs as a risk factor for HIV infection reflects the current epidemiologic profile of AIDS in the state of São Paulo. A relevant fact is that in 5 of these cases paracoccidioidomycosis was the first disease diagnosed or even the disease that induced the investigation of HIV infection. In 4 patients, paracoccidioidomycosis was apparently limited to the lungs with uncommon presentation in two of them, but in the remaining 3 it was generalized, with particular involvement of the monocyte-macrophage system and with multiple skin lesions characteristic of the acute-subacute forms of the clinical classification of paracoccidioidomycosis[7]. In the cases submitted to histopathological study, we detected an eminently exudative inflammatory response, loose granulomas and exuberance of fungal cells demonstrating the inefficient cell immune response. The therapeutic results may be considered effective for most patients, with emphasis on the need to introduce amphotericin B in two cases in order to obtain clinical resolution.

TABLE 1
Paracoccidioidomycosis and AIDS. Epidemiologic data.

Case Nº	Age	sex	HIV Epidemiology	*P. brasiliensis* Epidemiology
1	19	F	I.V. Drug Use	Undetermined
2	46	F	I.V. Drug Use	Undetermined
3	28	M	Bisexual	Undetermined
4	31	M	Heterosexual	Ex-Farmer
5	28	M	I.V. Drug Use	Farmer
6	25	M	I.V. Drug Use	Farmer
7	42	M	Homosexual	Undetermined

i.v. = intravenous

Epidemiologically, five of the patients were not involved in rural activities at the time of diagnosis, a fact suggesting the reactivation of quiescent foci of *P. brasiliensis* infection. Only one patient showed CD4 cell counts at diagnosis (67 cells/mm^3). Since few reports of this kind are available in the literature, the extent of HIV-induced immunosuppression necessary for, or contributing to, the manifestation of paracoccidioidomycosis as a disease still needs to be clarified. Finally, we emphasize that the number of cases of paracoccidioidomycosis-AIDS association may be less expressive than the histoplasmosis-AIDS association because of the generalized use of anti-*P. carinii* chemoprophylaxis with cotrimoxazole, a drug known to be effective against *P. brasiliensis*.

RESUMO

Paracoccidioidomicose associada à Síndrome da Imunodeficiência Adquirida. Relato de Sete Casos.

São apresentadas as características clínicas e evolutivas de sete pacientes (cinco masculinos e dois do sexo feminino), a maioria dos quais usuários de drogas ilicitas endovenosa, com paracoccidioidomicose associada à Síndrome da Imunodeficiência Adquirida (SIDA/AIDS). Em quatro pacientes a paracoccidioidomicose comprometia os pulmões isoladamente, nos demais a doença era generalizada com envolvimento cutâneo. Apenas dois pacientes eram procedentes recentes da zona rural. O que nos faz presumir que nos demais a paracoccidioidomicose doença resultou da reativação de focos latentes da infecção. Dado o papel da imunidade medida por células na defesa do hospedeiro contra o *Paracoccidioides brasiliensis*, é de se prever crescente ocorrência da associação paracoccidioidomicose - SIDA/AIDS nas áreas endêmicas para ambas as enfermidades.

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