

CLINICAL AND SEROLOGIC FEATURES OF 47 PATIENTS WITH PARACOCCIDIOIDOMYCOSIS TREATED BY AMPHOTERICIN B

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S U M M A R Y

In the present study, clinic and serologic aspects of 47 paracoccidioidomycosis patients were reviewed. The clinic-radiologic-laboratorial data of each patient were obtained from the medical chart before, during and after therapy with Amphotericin B. The age of the patients ranged between 13 to 50 years; the ratio male: female was 10:1. The most frequently associated diseases were alcoholism and tabagism; tuberculosis was present in 14.2% of the cases. Most patients came from Botucatu of adjacent towns (central area of the State of São Paulo). Cough with sputum production, dyspnea and anorexia were the most frequent clinic manifestations. All 47 patients, but 5 presented pulmonary involvement which showed the radiologic pattern of interstitial exudate nodular type and fibrocicatritial lesions in 85.7%. There was associated emphysema in 37.7% of the patients. Blood urea, creatinin and kaliemia increased during therapy with Amphotericin B. Clinic-laboratorial follow-up showed electro-cardiographic changes in 13, hypertension in 9 and hyporreactivity in Thorn test in 1 patient. Complement fixation was the best serologic test for monitoring patients with paracoccidioidomycosis. Incomplete dosage of Amphotericin B led to therapeutic ineffectiveness.

I N T R O D U C T I O N

Paracoccidioidomycosis, also known as LUTZ, SPLENDORE and ALMEIDA's disease, is caused by *Paracoccidioides brasiliensis* (*P. brasiliensis*), a widely diffuse fungus in nature. Contamination appears to occur most frequently by inhalation, with installation of the fungus in the lungs, followed by lympho-hematogenic dissemination 1,2,16,18,19,21,22.

The main therapy utilized in our practice for the treatment of the disease is Amphotericin B, a toxic drug that requires long periods of patients hospitalization for the administration 3,9,10,16,21,22,23.

Lutz mycosis is one of the most widespread chronic lung diseases encountered in our region, which accounts for the largest number of admissions to the "Parasitic and Infectious Diseases Ward" of the Faculty of Medicine of Botucatu. Thus, the objective of the present paper was to report on our experience on some aspects of the clinical-serologic follow-up of patients with paracoccidioidomycosis.

MATERIAL AND METHODS

A study was carried out on 47 patients with paracoccidioidomycosis admitted to the

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Parasitic and Infectious Diseases Ward of the Faculty of Medicine of Botucatu and later followed on an out-patient basis. All patients had never received specific treatment. They were distributed by professional activities, age range, race, life habits and place of origin. An attempt was made to establish the duration of the disease from the first symptoms shown by the patient up to his hospitalization.

The clinical forms of the disease were identified on the basis of clinical data and subsidiary tests. The potassium and sodium levels were determined by photometric measure⁶ (normal range: potassium = 3.5 — 5.5 mEq/l; sodium = 135 — 148 mEq/l). The most apparent clinical manifestations were recorded. X-ray detected pulmonary lesions were classified as interstitial and/or alveolar according to their location. Etiologic diagnosis was made by direct mycologic examination and/or biopsy. Changes in laboratory tests observed before, during and after specific treatment were recorded.

All patients were submitted to the Thorn test¹³ and to electrocardiogram before, during and after treatment. A laboratory profile was determined on the basis of tests carried out during the various phases of Amphotericin B use. The drug was administered every other day at the dose of 1 mg/kg body weight. Total dose for each patient, 30 mg/kg body weight, varied from 1.5 to 2.0 g. This antifungic dose administered in two different moments for the same patient was considered as two complete doses. The drug was intravenously and slowly infused together the 5% glucose solution

through as Y connection. Corticoid were not associated to the Amphotericin B treatment. Toxic side effects were recorded. The following serologic tests were applied: complement fixation (CF)¹¹, tube precipitin (Tp)¹¹ and indirect immunofluorescence (II)¹⁴. An evolving serologic profile was constructed for each patient after treatment with Amphotericin B and during follow-up at the out-patient clinic.

Patients were considered cured when clinical examination and laboratory tests did not show any evidence of disease for a minimum period of one year after treatment. Late side effects caused by treatment were recorded.

RESULTS

Thirty-six of the 47 patients were farm laborers. Age range was 13 to 50 years. Male white subjects predominated by a 10:1 ratio. The habits most often reported was addiction to tobacco (35 patients) and to alcohol (25 patients). Most of the patients were originated from towns near Botucatu.

Duration of the disease was 6 months in 23 and 7 to 36 months in 16 of them. The general clinical, digestive and respiratory symptoms reported by the patients are presented in Table I.

The clinical forms of paracoccidioidomycosis were: pulmonary in 3 patients, lymphoadenitic in 4, and mixed in 40. The mixed forms consisted mainly of tegumentary-pulmonary and lymphatic-tegumentary-pulmonary involvement. Clinical examination showed tegumentary le-

T A B L E I
General clinical, digestive and respiratory manifestations

General	No.	Clinical manifestations		Respiratory	No.
		Digestive	No.		
Weight loss	36	Vomiting	12	Expectorating cough	37
Anorexia	27	Nausea	8	Dyspnea	23
Fever	18	Dysphagia	7	Hyaline expectoration	21
Weakness	14	Pyrosis	5	Hoarseness	18
Indisposition	14	Abdominal pain	4	Mucopurulent cough	15
Cephalaea	12			Hemoptoic cough	11
Shivering	8	Constipation	4	Dry cough	10
Sudoresis	8	Jaundice	4	Chest pains	9
Palpitation	5			Wheezing	4
Dizziness	4				
Visual alterations	4				
Ascites	2				
Cramps	1				

sions in 19 patients, adenopathy in 16, hepatomegaly in 15, hepatosplenomegaly in 8, and stomatitis in 6. The most frequent locations of the tegumentary lesions are reported in Table II. On the whole, the severity of the disease was documented by the great number of mixed forms, the rapid progression of symptomatology and by the intense general clinic and/or pulmonary manifestations.

T A B L E II
Location of the tegumentary lesions

Oropharynx	24
Face	5
Limbs	4
Nose	2
Chest	2
Scalp	1
Neck	1

Five patients (10.6%) showed no radiologically detectable lung lesions. Radiologic examinations of the pulmonary lesions revealed predominance of interstitial exudates (85.7%), especially of the nodular and fibrotic types. Bilateral parahilar distribution of the lesions was observed in 32 of the 42 patients. Changes in

the carinal angle and hilus of the pulmonary artery were observed in 66.6% of cases. Pulmonary emphysema was observed in 17, indirect signs of pulmonary hypertension in 4, and pleural involvement in 3 patients. Association with tuberculosis was confirmed in 6 of 9 patients who presented apical cavities.

Etiologic diagnosis of paracoccidioidomycosis was made by direct mycologic examination of the tegumentary lesions in 12 patients, of the sputum in 10, and of ganglionic secretion in 5. The etiology of the process was defined histologically in 22 patients, by lymph node biopsy in 10, skin and mucosa biopsy in 10, liver biopsy in 1 and knee joint biopsy in 1 case.

Laboratory changes at admission and the collateral effects caused by Amphotericin B are presented in Table III and IV, respectively. It is noteworthy that 15 patients presented mild to moderate hyperkalemia during therapy with values ranging from 5.6 to 6.8 mEq/l. The therapeutic results were evaluated clinically and serologically in 35 patients 6 months to 6 years after treatment (Table V). Clinical and serologic cure occurred in 54% of all patients.

T A B L E III
Laboratory changes upon admission

Hemogram				Biochemical tests			
Decrease	No.	Increase	No.	Decrease	No.	Increase	No.
Lymphocytes	24	S.H.S.	28	Albumin	15	Globulin	19
Red blood cells	16	Leucocytes	26	Thorn test	3	Mucoprotein	15
Leucocytes	3	Eosinophils	22			Kalemia	14
		Neutrophils	20			Urea	11
		Reticulocytes	11			Alkaline phosphatase	10
						Thymol turbidity	8
						Oxaloacetic T.G.	6
						Pyruvic T.G.	6
						Total protein	4

The following late clinical and laboratory changes were detected: electrocardiographic alterations in 13 patients; incomplete blockage of the right branch in 2; hypokalemia in 10; left ventricular overload in 1; bradycardia in 2 and pericarditis and/or hyperkalemia in 1; arterial hypertension in 9, 5 of whom had decrease creatinine clearance with hyperkalemia; hyporeactive response to the Thorn test in 1 together with clinical signs of adrenal insufficiency. Hemoglobin, white cells and lymphocytes counts improved.

Evolving radiologic evaluation of 25 patients with lung involvement showed: persistent interstitial exudative lesions, calcified nodules and residual fibrosis in 22, and improvement in 3 patients.

DISCUSSION

In the present study, the higher incidence of the disease among white farm laborers, aged 21 to 50 years, with males outnumbering women 10 to 1 represent findings that are simi-

T A B L E I V
Collateral effects caused by Amphotericin B

Increased urea	29
Increased creatinine	23
Hyperkalemia	14
Hypokalemia	12
Decreased creatinine clearance	4
Digestive changes	11
Flebitis	10
Acute hemorrhagic ulcer	1
ECG changes	9
Tachycardia	2
Bradycardia	2
Cardiotoxicity	1
Focal pericarditis	1

T A B L E V
Therapeutic results in 35 patients treated with Amphotericin B (1 or 2 complete doses) evaluated in terms of clinic-serologic evolution (Follow-up of 6 months to 6 years)

Number of complete doses	Number of patients Clinical-serologic evaluation			
	1	2	Unchanged ^a Improvement Cured	
12	6	5	2	11
Incomplete dose				
	17	11	3	3
Total =	35	16	5	14
	(%)	(46)	(14)	(40)

lar to those obtained by other investigators 1,3, 16,17,18,21,22,23. The patients came from towns near Botucatu which seem to have ecological peculiarities that favour the development of *P. brasiliensis* 20.

Mixed forms were observed in 85.1% of all patients, a fact suggesting that in the present sample the disease tended to disseminate or to have early systemic characteristic. The tegumentary lesions were always associated with the involvement of other organs or systems, as reported by other investigators 4,18. The general clinical, respiratory and digestive manifestations agreed with those reported by others 3,4,10,16. Dyspnea, dry or loose cough, especially of the hemoptoic type occurred more frequently than reported in the literature 3,4,10, 16,17. A noteworthy occurrence was clinical jaundice observed in four patients, indicating a possible specific involvement of the portal spaces and/or lymph nodes of the hepatic hilus 4,10,16.

The following unusual clinical presentations should be mentioned: pseudotumoral esophageal form associated with cavities in the

lung apex 27 and excavated paracoccidioma in the middle lobe of the right lung 12,17,21.

In general, the results of the lung X-rays agreed with those reported by LIMA 17: predominance of interstitial lesions, bilateral parahilar lesions with changes in the carinal angle and hilus of the pulmonary artery. The presence of lung emphysema in 40.4% of the patients may have been partially due to the high frequency of smoking.

The association of pulmonary paracoccidioidomycosis with tuberculosis has been reported by several authors, with incidences of 5.4 to 21.4% 12,16,17,18,21. In the present sample, the incidence was 14.2%. When apical cavities are encountered by chest X-rays in our patient population, it is obligatory to exclude tuberculosis. On the other hand, lung cavities due to paracoccidioidomycosis have been reported in the literature 4,12,17,21. It is interesting to point out that 3 of our patients had hilar nodules similar to those caused by lung tuberculosis. Pulmonary changes similar to those of the primary tuberculosis complex have been recently reported in studies on paracoccidioidomycosis 24,25.

Etiologic diagnosis was confirmed in all patients studied here either by examination of the secretion or by biopsy of the lesions. With respect to the technique for the detection of *P. brasiliensis* in sputum, we would like to point out the cytoinclusion method recently standardized in our hospital, which permits establishing prompt etiologic diagnosis in most cases 15.

In agreement with reports by other investigators, the most frequent changes shown by laboratory tests upon patient admission were: high globulin and mucoprotein levels, possibly due to the chronic inflammatory process; hyperkalemia and increased urea levels due to augmented catabolic activity; increased alkaline phosphatase either because of specific hepatic involvement or hypersensitivity reaction to *P. brasiliensis*. Decreased serum albumin levels were observed in 32% of the patients, possibly due to an association of multiple factors such as malnutrition, verminoses and lymphatic changes caused by the disease.

The hyporeactive response to the Thorn tests in 7 patients showed the usefulness of this

test for determining adrenal involvement in paracoccidioidomycosis^{7,8}. A study was carried out in our hospital on patients admitted with active and recent paracoccidioidomycosis showed hyporeactive responses to the test⁷, suggesting that adrenal involvement may occur early in the disease.

The hyperkalemia observed during treatment may be explained by different mechanisms^{5,6,13}; the action of the drug on the tubules may be sufficient to damage them and prevent sodium-potassium ion exchange; the alteration of the sodium-potassium relationship may be the expression of functional or organic adrenal insufficiency; decreased arterial renal flow caused by the drug leading to oliguria (pre-renal azotemia) and potassium retention; lung involvement by the mycosis leading emphysema and respiratory acidosis interfering with the adequate renal sodium-potassium ion exchange.

Some electrocardiographic changes encountered in 13 patients, such as incomplete blockage of the right branch, bradycardia, and pericarditis may indicate that the drug is cardiotoxic. However, as previously reported in the literature, Amphotericin B does not seem to cause irreversible lesions of cardiac fibers. These changes may be partly explained by factors associated with patient age^{23,26}. Ten of the 42 electrocardiographic exams exhibited hypokalemia.

Complement fixation was the best test for determining cure or improvement of patients. Serologic worsening coincided with absence of clinical cure. Evolving radiologic analysis of 25 patients showed nodules and residual pulmonary fibrosis in most cases^{12,22,24}.

Evolving clinical-serologic evaluation demonstrated that the use of incomplete doses of Amphotericin B frequently resulted in unsuccessful treatment. On the other hand, in comparison to our data, Amphotericin B used in doses higher than 2 g has shown similar cure percentage and increased toxicity, specially nephrotoxicity¹⁰.

Amphotericin B used in doses higher than 2 g and in more intensive schemes as compared to there of the present work has been reported to show similar rate of clinical cures and in-

creased rate of collateral effects, specially nephrotoxicity¹⁰.

RESUMO

Aspectos clínicos e sorológicos de 47 pacientes com paracoccidioidomicose tratados pela anfotericina B

No presente trabalho, foram avaliados 47 doentes com paracoccidioidomicose. Utilizou-se ficha padronizada que continha todas as informações clínicas, radiológicas e laboratoriais dos doentes antes, durante e após terapia pela anfotericina B. Os resultados mostraram que a faixa etária oscilou entre 13 a 50 anos com predomínio do sexo masculino (10:1). O tabagismo e o etilismo foram os antecedentes mais referidos. Os doentes provieram de municípios vizinhos de Botucatu. Tosse expectorativa, dispnéia, emagrecimento e anorexia foram as manifestações clínicas mais assinaladas. A forma mista predominou. Cinco pacientes não apresentaram lesões pulmonares. Nos demais 42 pacientes, a radiologia pulmonar revelou exsudatos intersticiais dos tipos nodular e fibrocicatricial em 85,7%, enfisema pulmonar em 37,7% e associação com tuberculose em 14,2% dos casos.

A elevação da uréia, creatinina e do potássio foram as alterações laboratoriais mais frequentes decorrentes do uso de anfotericina B.

A avaliação clínico-laboratorial tardia mostrou: alterações eletrocardiográficas em 13; hipertensão arterial em 9 e resposta hiporreatora ao teste de Thorn em 1 doente.

A reação de fixação do complemento foi o teste sorológico que melhor se prestou para estabelecer o critério de cura.

O insucesso terapêutico coincidiu com o emprego da dose incompleta da anfotericina B.

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REFERENCES

1. ALBORNOZ, M. B. — Paracoccidioidomycosis: estudo clínico y inmunológico en 40 pacientes. *Arch. Hosp. Vargas (Caracas)* 18: 5-22, 1976.

2. ANGULO ORTEGA, A. — Las micosis bronco-pulmonares en el Departamento de Anatomía Patológica del Instituto Nacional de Tuberculosis. *Rev. Tisiol. Neurol.* 1: 101-108, 1959.
3. AZEVEDO, J. F. & LISBOA, C. — Paracoccidioidomycose: estudo de 106 casos. *J. Pneumol.* 6: 30-33, 1980.
4. BRASS, K. — Observaciones sobre la anatomía patológica, patogénesis y evolución de la paracoccidioidomycosis. *Mycopathologia* (Den Haag) 37: 119-138, 1969.
5. BURGESS, J. L. & BIRCHALL, R. — Nephrotoxicity of Amphotericin B, with emphasis on changes in tubular function. *Am. J. Med.* 52: 77-83, 1972.
6. BURINI, R. C. & CAMPANA, A. O. — Padronização da metodologia para análise do sódio e do potássio em soluções eletrolíticas semelhantes ao plasma pela fotometria de chama. *Rev. Bras. Pesq. Med. Biol.* 3: 25-36, 1970.
7. CAMPOS, E. P.; CARNEIRO, A. C.; RAMOS, M. D.; MENDES, R. P. & MEIRA, D. A. — Avaliação da função supra-renal na vigência do tratamento da blastomicose sul-americana pela Anfotericina B. *Anais da V Jornada Científica da Faculdade de Ciências Médicas e Biológicas de Botucatu*, p. 74, Botucatu, 1975.
8. DEL NEGRO, G. — *Localização supra-renal da blastomicose sul-americana*. São Paulo, Saraiva, 1961. [Tese — Livre-Docência — São Paulo].
9. DEL NEGRO, G. — Tratamento da paracoccidioidomycose. *Ars Curandi* 7: 38-44, 1975.
10. DILLON, N. L. — *Tratamento da paracoccidioidomycose pela Anfotericina B. Avaliação de 119 doentes num período de 14 anos*. São Paulo, 1972. [Tese — Doutorado — Faculdade de Medicina da Universidade de São Paulo].
11. FAVA NETTO, C. — Estudos quantitativos sobre a fixação do complemento na blastomicose sul-americana, com antígeno polissacarídeo. *Arq. Cirurg. Clin. Exp.* 18: 197-254, 1955.
12. FIALHO, A. S. — *Localizações pulmonares da "Micose de Lutz"*. *Anatomia patológica e patogenia. Importância de seu estudo na patologia pulmonar*. Rio de Janeiro, 1946 [Tese].
13. FORSHAM, P. H. & KENNETH, L. — Supra-renales. In: WILLIAMS R. H. — *Tratado de Endocrinologia*. 3.ª ed. Barcelona, Sabat Editores, 1973, cap. 5, p. 289-408.
14. FRANCO, M. F.; FAVA NETTO, C. & CHAMMA, L. G. — Reação de imunofluorescência indireta para o diagnóstico sorológico da blastomicose sul-americana. Padronização da reação e comparação dos resultados com a reação de fixação do complemento. *Rev. Inst. Med. trop. São Paulo* 15: 393-398, 1973.
15. IWAMA DE MATTOS, M. C. F. — Cell-block preparation for cytodagnosis of pulmonary paracoccidioidomycosis. *Chest* 75: 212, 1979.
16. LACAZ, C. da S. — *Compêndio de Micologia Médica*. 5.ª ed. São Paulo, Sarvier, 1973, p. 229-271.
17. LIMA, F. X. P. — *Contribuição ao estudo clínico e radiológico da blastomicose pulmonar*. São Paulo, 1952. [Tese — Doutorado — Faculdade de Medicina da Universidade de São Paulo].
18. LONDERO, A. T. & RAMOS, C. D. — Paracoccidioidomycosis. A clinical and mycologic study of forty-one cases observed in Santa Maria, R.S., Brazil. *Amer. J. Med.* 52: 771-775, 1972.
19. MACKINNON, J. E. — Blastomycosis sul-americana experimental evolutiva por via pulmonar. *An. Fac. Med. (Montevideo)* 44: 355-358, 1959.
20. MARQUES, S. A.; FRANCO, M. F.; MENDES, R. P.; SILVA, N. C. A.; BACCILLI, C.; CURCELLI, E. D.; FERACIN, A. C. M.; OLIVEIRA, C. S.; TAGLIARINI, J. V. & DILLON, N. L. — Aspectos epidemiológicos da paracoccidioidomycose na área endêmica de Botucatu (São Paulo — Brasil). *Rev. Inst. Med. trop. São Paulo* 25: 87-92, 1983.
21. PARACOCIDIIDOMYCOSIS — Scientific Publications. *Pan American Sanitary Bureau* 254: 101-125, 1972.
22. RESTREPO, A. — Paracoccidioidomycosis. In: FEIGIN, R. D. & CHERRY, J. D. — *Text Book of Pediatric Infectious Diseases*. Philadelphia, W.B. Saunders, 1981, V2, cap. 34, p. 1500-1505.
23. SAMPAIO, S. A. P. — *Tratamento da blastomicose sul-americana com Anfotericina B*. São Paulo, 1960. [Tese — Cátedra — Universidade de São Paulo].
24. SEVERO, L. C. — *Paracoccidioidomycose. Estudo clínico e parasitológico das lesões pulmonares e seu diagnóstico*. Porto Alegre, 1979. [Tese — Mestrado — Universidade Federal do Rio Grande do Sul].
25. SEVERO, L. C.; PALOMBARINI, B. C.; UTZ, E. & BRAUN, S. N. — Paracoccidioidomycose pulmonar resultante da reativação de foco quiescente em paciente imunossuprimido. *J. Pneumol.* 6: 21-22, 1980.
26. TREZZA, E.; DILLON, N. L. & CAMPOS, E. P. — Alterações eletrocardiográficas durante o uso da Anfotericina B. In: *Congresso Brasileiro de Cardiologia*, p. 28, Curitiba, 1972.
27. ZILLOTTO JÚNIOR, A.; KUNZLE, J. E. & TAKEDA, F. A. — Paracoccidioidomycose em esôfago. Apresentação de um caso. *Rev. Inst. Med. trop. São Paulo* 22: 261-264, 1980.