Rev. Pat. Trop. 12(3): 295-305, set./dez. 1983

HEPATIC INVOLVEMENT IN PARACOCCIDIOIDOMYCOSIS***

William Barbosa * *e Ana Lúcia S. S. Andrade* **

SUMMARY

Paracoccidioidomycosis involves the liver and/or the bile ducts in a considerable number of patients with the acute disseminated form of the disease in the lymphatic abdominal type. It may produce fatty degenerative changes in the hepatic parenchyma, acute hepatitis, chronic granulomatous hepatitis, moderate portal fibrosis and occasionally marked necrosis. These changes are accompanied by jaundice. Frequently obstrutive extrahepatic jaundice dominates the clinical manifestations.

INTRODUCTION

South American Blastomycosis, at present called paracoccidioidomycosis, is a systemic mycosis caused by P. brasiliensis. Two clinical forms are encountered: a) one clinical form occurs in patients who have had multiple past microinfections by mildly virulent strains along many years, probably dating back to their first decade of life or they might have been infected by saprophytic fungi with some antigenic similarity and have thus developed some immunity against P. brasiliensis. Such patients acquire the infection most frequently by inhalation and have some pulmonary involvement. The disease may remain asymptomatic in many cases. Frequently there is lymph node, throat and skin involvement. It may run a chronic course with relapses until the third or fourth decade of life when the disease is diagnosed. When patients receive adequate treatment, they may live until the age of sixty or longer. This cli-

* Dept. of Tropical Disease – IPT – UFG
** Dept. of Preventive Medicine – IPT – UFG
*** Trabalho realizado com Apoio do FINEP

nical form is called: chronic disseminated form of paracoccidioidomycosis. b) The other clinical form, on the contrary, occurs "ab initio" with no previous immunity. It is an acute and disseminated form which is prevalent in young patients under twenty years of age. For some unknown reason, in this clinical disseminated form which always presents extensive lymph node elargement, there is no pulmonary involvement whereas in the chronic form there is an outstanding lung involvement. In the acute form there is widespread involvement of the abdominal organs: lymph nodes, intestine, spleen, liver and bile dusts. In this clinical form the fungus probably penetrates the lower extremities following injury to the skin. This special clinical form with widespread involvement of lymph nodes and many abdominal viscera we call lymphatic abdominal form or acute disseminated form. The disease is characterized by several syndromes which may appear associated. The most important are: diarrhea, severe malabsorption syndrome, intestinal subocclusion, intestinal obstruction, hepatosplenomegaly, jaundice, hepatitis, ulcerative colitis and regional ileitis. (13, 16)

As it can be seen, in this clinical form, called by some authors acute disseminated form of young patients and also known as juvenile form of paracoccidioidomycosis, the liver and bile ducts are involved.

In 1913, (24) Gaspar Viana reported for the first time the hepatic involvement in this disease; Cunha Motta (9) in his revision of necropsy material of the Hospital das Clinicas of the University of S. Paulo observed the high incidence of hepatic involvement.

From the clinical point of view we will approach the subject considering: 1.) Isolated hepatomegaly which is a more frequent finding and is milder: 2.) Jaundice which has almost always a poor prognosis.

Hepatomegaly

In paracoccidioidomycosis, hepatomegaly is almost always accompanied by splenomegaly and reticuloendothelial system hyperplasia. Silva and Campos, (21, 22) reported three cases presenting this clinical picture with extensive involvement of peripheric lymph nodes and called attention to the differential diagnosis with Hodgkin's disease.

Although not enough emphasis has been laid upon this aspect, liver enlargement may be found or suspected in most cases described with lymphatic abdominal form.

In Castro's, (7) cases, 50% of the patients presented hepatomegaly among the 10 cases reported by Boccalandro and Albuquerque, 80% had liver enlargement. In 11 cases studied by one of us in 1968 (3, 4), we found only 20% of hepatomegaly. In 87 cases revised by Fonseca and Mignone (13) with small intestine involvement, 26,8% had hepatic enlargement.

Jaundice

Jaundice is one of the manifestations shown by severe cases of paracoccidioidomycosis. Among nine patients with jaundice studied by us in 1973, (10) seven ran a fatal course. Reports from S. Paulo also showed high mortality rates in cases with jaundice.

BARBOSA, W.; ANDRADE, A.L.S.S. Hepatic involvement in paracoccidioidomycosis. Rev. Pat. Trop. 12(3): 295-305, set./dez. 1983.

In extrahepatic bile duct obstruction syndromes which had been hurriedly misdiagnosed as due to neoplasm, the finding of P. brasiliensis is not rare at post mortem examination.

Three basic mechanisms are responsible for the appearance of jaundice in paracoccidioidomycosis (2, 3, 5, 7, 10, 14, 18, 20): 1) Extrinsical compression by lymph nodes or stretching by fibrosis; 2) Intraluminar granulomatous lesion of the common bile duct; 3) Hepatic lesion caused by the blastomycotic hepatitis.

In patients with extrahepatic bile duct obstruction, hepatic transparieto percutaneous cholangiography has been used sucessfully. It brings into view infiltration or extrinsical compression of the bile ducts thus providing valuable information to diagnosis. (8)

The chief pathologic changes found in the livers of numerous post mortem examinations or in liver biopsy studies are well known: granulomatous hepatitis, with or without the presence of P. brasiliensis; parenchymatous hepatitis, portal fibrosis with the presence of P. brasiliensis; only granulomas containing the parasite and extrahepatic cholestasis; Kuppfer ceil hyperplasia and fatty parenchymatous infiltration of the liver. (5, 6, 7, 10, 12, 15, 19)

In contrast with these findings, there are also descriptions of extensive hepatic lesions with areas of necrosis and disarrangement of the hepatic parenchyma.

Brito (6) studied 22 cases of paracoccidioidomycosis. Liver biopsies were taken and hepatic changes were distributed into three groups:

A) Not specific lesions characterized by reticuloendothelial hyperplasia.

B) The same findings as in group A plus intransinusoidal granulomas.

C) Portal granulomas with central necrosis containing a large number of parasites which destroy focally the limiting lobular membrane.

In the lynphatic abdominal form, liver involvement may occur during the phase of hematogenic dissemination, chiefly through the portal vein or by continuity. Daher (10) observed a productive granulomatous inflamatory process, chiefly portal which appeared sussounding the granulomas. The exudative process may compress the interlobular bile ducts causing little cholestasis. The author also reports marked reticuloendothelial hyperplasia and emphasized the presence of large numbers of parasites which facilitate the diagnosis.

Recently, Pinto (19) performed liver biopsies in patients with several clinical forms. He found the following changes in three patients with intestinal involvement: chronic neutrophilic inflamatory infiltration in two patients and eosinophilic infiltration in the third; all had portal fibrosis and reticuloendothelial hyperplasia; one patient had hepatocelular lesion without granuloma; the other two patients showed intralobar sacarring and granulomas; one patient presented central necrosis. In none of these patients P. brasiliensis was found.

Biochemical changes

In all granulomatous diseases including paracoccidioidomycosis with or whithout liver involvement, there may be an increase insealkaline phosphatase.

In patients with jaundice, the laboratory findings are those of cholestasis with hyperbilirubinemia with predominant increase in conjugated bilirubin, hypercholesterolemia and increase in alkaline phosphatase.

As it may be seen in most cases of extrahepatic biliary obstruction, serum transaminases are moderately increased. In general these cases are observed in patients with lymphatic abdominal involvement. Impairment of vitamin K absorption and consequent decrease in plasma prothrombin has also been reported.

Material and methods

The clinical is the same that was used in a recent analysis of 57 cases with lymphabdominal form which were observed from 1968 to 1980 at the Department of Tropical Medicine. The cases were reported by one of us (1) in a Theses. We studied the liver involvement with special emphasis on the physiopathology of jaundice and hepatomegaly. Besides the habitual clinical observations, we resorted to investigations, such as biochemical determinations, hemogram, electrophoresis of serum proteins, serum enzyme determinations. In all cases we also performed X ray, histopathologic and immunologic studies.

Results

Table I focuses the clinical findings. The patients were acutely ill, their disease had an average evolution of four months. Among the 57 patients, 34 (59,6%) showed hepatomegaly and 13 (22,8%) had jaundice.

As to jaundice, in 11 patients (84,6%) it appeared early in the course of the disease and before beginning of treatment; in two patients (15,4%) jaundice appeared late. One case of jaundice was concomitant with malaria by P. falciparum (relapse); In one patient, jaundice appeared post-operatively after exploratory laparotomy.

In 6 cases, the cause of jaundice was not rigorously identified. In the remainning 7 cases, the causes were identified. In the remaining 7 cases, the causes were identified through exploratory laparotomy – 4 cases, liver biopsy – 2 cases, laboratory examinations – 1 case; hepatic transparieto cholangiography documented 2 of these cases. TABLE 2.

In 34 cases of this series, (59,7%) hepatomegaly was present; It was moderate in 16, slight in 9 and marked in 9 patients. Twelve patients had concomitant hepatomegaly and jaundice.

The histopathological hepatic findings of 12 cases (9 were submitted to liver biopsy and 3 to necropsy) are found in Table III and can be summed up in the following way: no hepatic changes, 4 cases (33,3%); with hepatic changes – 8 cases (66,7%). Chronic granulomatous hepatitis with the presence of P. brasiliensis was found in 3 patients (37,5%), acute hepatitis by P. brasiliensis with focus of granulomatous reaction in 2 (25%) and extrahepatic cholestasis in 2 (25%).

The results of Transaminase determinations were not very expressive; the highest values of GOT and GPT were, respectively 250 U/ml and 340 U/ml (Reitman-Frankel) both figures were obtained in cases with jaundice, one patient had chronic granulomatous hepatitis by P. brasiliensis, the other patient had extrinsecal obstruction of the common bile duct by adenites as was confirmed by exploratory laparatomy. 14 patients (32,5%) showed and increase in GOT – nine of these patients had jaundice. Nine out of eleven patients with an increase in GPT had jaundice. Among the 13 icteric patients, increase of total, direct and indirect bilirubin values were observed in 10 patients. Alkaline phosphatase and cholesterol were increased in two and three patients respectively. In one of the patients with jaundice who had intrinsic common bile duct obstruction, the value of serum alkaline phosphatase reached 38,3 U/ml (Bessey/Lowry).

BARBOSA, W.; ANDRADE, A.L.S.S. Hepatic involvement in paracoccidioidomycosis. Rev. Pat. Trop. 12(3): 295-305, set./dez. 1983.

TABLE I – Digestive signs and symptoms reported and/or identified in 57 patients with lymphatic abdominal paracoccidioidomycosis

Signs and Symptons	Patients	
	Number	%
Abdominal pain	51	89,5
Abdominal mass	40	70,2
Diarrhea	36	63,2
Intestinal obstipation	21	36,8
Obstipation and diarrhea	12	21,0
Ascites	21	36,8
Jaundice	13	22,8
Hepatomegaly	34	59,6
Splenomegaly	24	42,1
Vomiting	27	47,4
Pyroris	5	8,8

Comments

In this series of 57 cases of lymphatic abdominal form of paracoccidioidomycosis, we found that jaundice was present in 22,8% of the cases. These results are compatible with the average findings registered in literature.

In almost all cases (84,6%) jaundice appeareared early. In 7 cases (53,8%) it was possible to identify the mechanism that caused jaundice. There was a predominance of the obstructive type over the parenchymatous type in the proportion of: 2:1. Similar results have also been found by other authors.

TABLE II – Mechanism of jaundice in 13 patients with lymphatic abdominal paracoccidioidomycosis

Mechanism of jaundice	Patients	
	Number	%
Not identified	6	46,2
Identified *	7	53,8
Extrinsic obstruction of the common bile duct	2	28,6
Intrinsic obstruction of the common bile duct	2	28,6
Acute hepatitis with P. brasiliensis and swelling of the hepatic hilum	1	14,3
Granulomatous hepatitis by P. brasiliensis	1	14,3
Associated with malaria	1	14,3
TOTAL	**13**	**100**

** The following procedures helped to confirm the mechanism responsible for jaundice: exploratory laparotomy in 4 patients; liver biopsy in 2 patients; laboratory examinations in 1 patient; cholangiography in 2 patients.*

Hepatomegaly was found in 59,7% of the cases. Most patients (47%) showed a moderate increase of the liver but in 26,5% of the cases hepatomegaly was marked. This expressive frequency of hepatomegaly, including the association with malaria in 3 cases, was much superior to that found by other authors who studied the digestive and/or lymphatic abdominal involvement in paracoccidioidomycosis.

12 out of 34 patients with hepatomegaly had jaundice. Hepatomegaly in icteric patients may be caused either by specific lesions of the liver or only by cholestasis. In patients without jaundice both the presence of granulomatous lesions and chronic passive congestion as well as reticuloendothelial hyperplasia, in the absence of specific lesion contribute to liver enlargement in paracoccidioidomycosis.

It must be pointed out that the finding of splenomegaly (42,1%) was less frequent than hepatomegaly, though it is well know by histopathologic studies that the spleen is almost always involved in this clinical form of the disease.

In histopathologic studies of 12 cases, changes were found in 8 cases and in 4 of them P. brasiliensis was present.

The finding of the fungus in 33 of our cases is more frequent than was reported by Pinto (19) who only found 3 in twenty biopsies. Perhaps this is due to the fact that we also work with post mor-

BARBOSA, W.; ANDRADE, A.L.S.S. Hepatic involvement in paracoccidioidomycosis. Rev. Pat. Trop. 12(3): 295-305, set./dez. 1983.

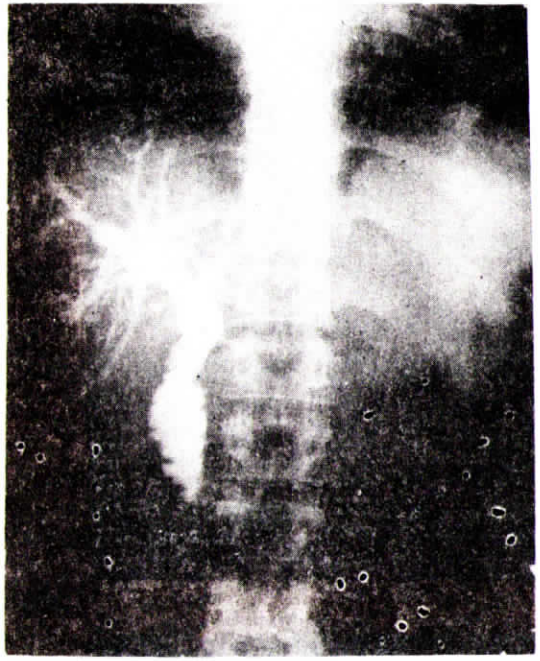

FIGURE I – Hepatic transparietal cholangiografy performed with a needle of "CHIBA", showing intrahepatic dilation and bowing of the biliary ducts in the right lobe of the liver; extrahepatic dilatation with portal obstacle at the distal portion of the common bile duct.

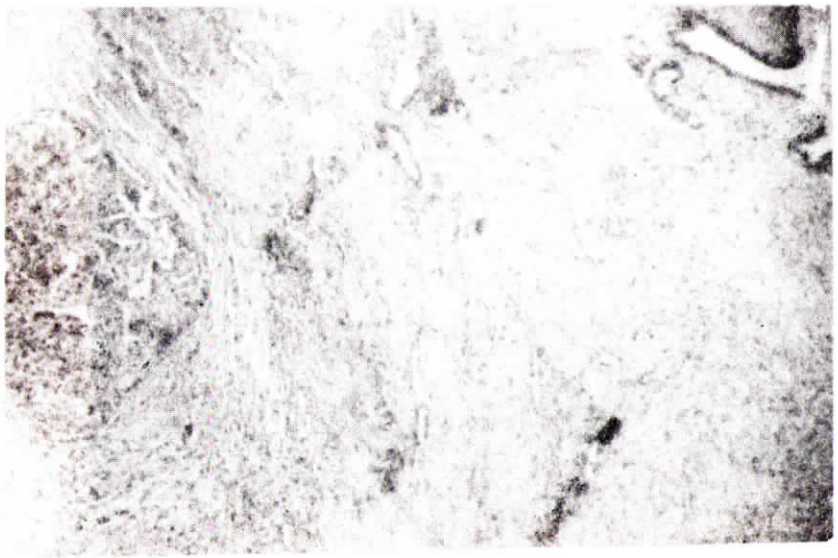

FIGURE II – Granulomatous lesion of the common bile duct in a patient with obstructive jaundice

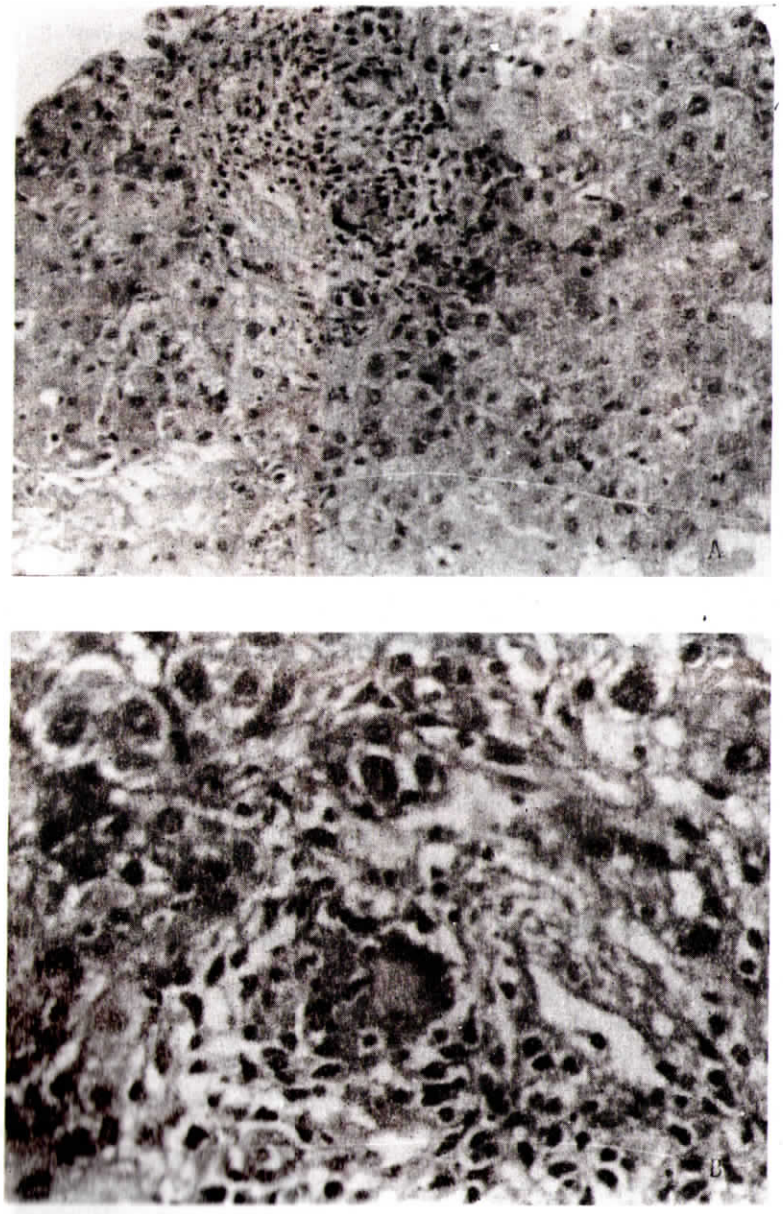

FIGURE III – Histopathology of the liver (SFO – case n. 35) showing granulomatous process with rare giant cells involving the portal space, respectively in lower (A) and higher (B) amplification

BARBOSA, W.; ANDRADE, A.L.S.S. Hepatic involvement in paracoccidioidomycosis. Rev. Pat. Trop. 12(3): 295-305, set./dez. 1983.

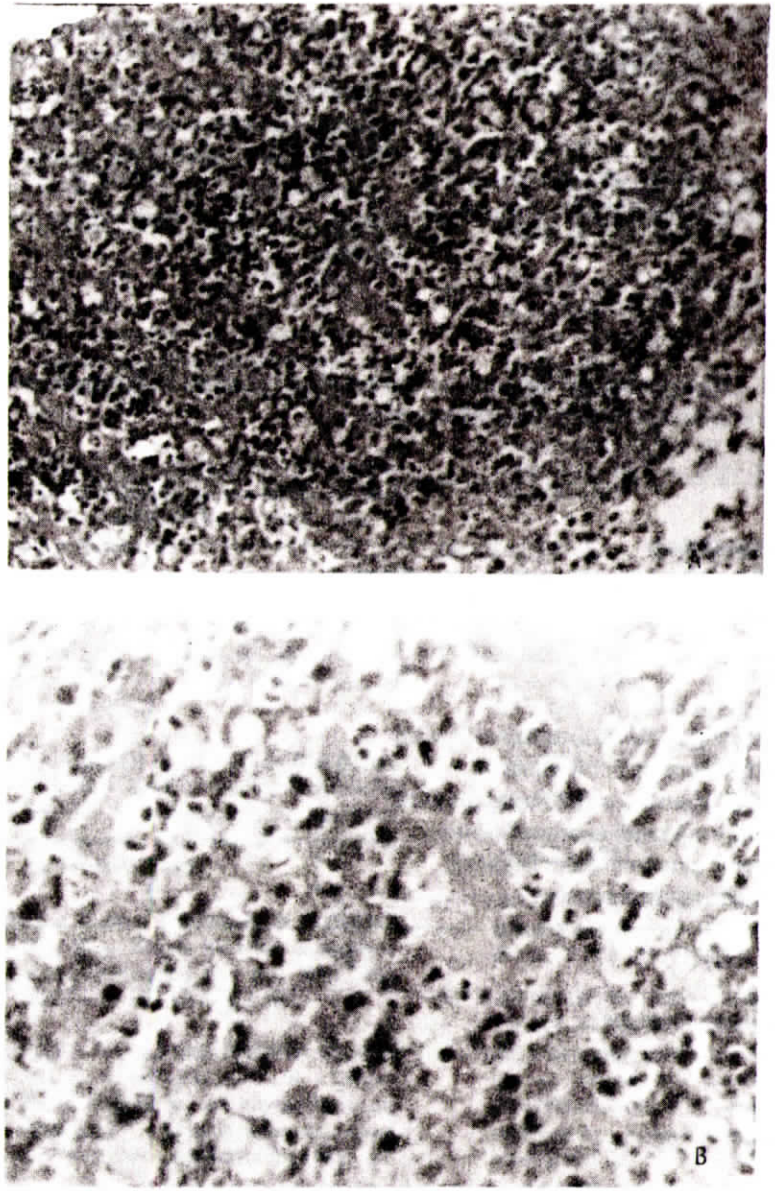

FIGURE IV – Histopathology of the liver (IFM – case n. 51) showing extensive areas of necrosis with large number of parasites (A and B)

tem material in which the frequency of findings of P. brasiliensis increases. Teixeira (23) found 57,6% in 60 cases at autopsy.

In our casuistic all cases in which P. brasiliensis was found were patients with jaundice.

In the 2 cases with chronic granulomatous hepatitis without fungus, no allergic correlation was found, exactly as was reported by Castro (7) and by Pinto (19) in their cases. The implication of granulomatous hepatic lesions due to drugs with hypersensitivity reactions is known.

TABLE III – Histopathologic diagnosis of the liver in 12 patients with lymphatic abdominal paracoccidioidomycosis

Liver histopathology	Patients	
	Number	%
No changes	4	33,3
With changes	8	66,7
Chronic granulomatous hepatitis with the presence of P. brasiliensis	3 *	37,5
Acute hepatitis by P. brasiliensis with focuses of granulomatous reaction	1 *	12,5
Chronic granulomatous hepatitis	2 *	25,0
Extrahepatic colestasis	2 *	25,0
TOTAL	12	100

* *Patients with jaundice.*

RESUMO

Comprometimento hepático na paracoccidioidomicose

A paracoccidioidomicose compromete o fígado e/ou as vias biliares em número considerável de pacientes na forma disseminada aguda da doença do tipo linfático-abdominal tendo sua tradução em processo degenerativo gordo do parênquima hepático, hepatite aguda, hepatite granulomatosa crônica, fibrose portal de pequena intensidade e ocasionalmente necrose acentuada, alterações essas concomitantes com icterícia e freqüentemente com icterícia obstrutiva extra-hepática que domina o quadro clínico.

BARBOSA, W.; ANDRADE, A.L.S.S. Hepatic involvement in paracoccidioidomycosis. Rev. Pat. Trop. 12(3): 295-305, set./dez. 1983.

REFERÊNCIAS BIBLIOGRÁFICAS

01. ANDRADE, A. L. S. S. – Paracoccidioidomicose linfático-abdominal – Contribuição ao seu estudo. Tese de Mestrado. IPT/UFG. 1983.

02. BARANSKI, M. C.; GOMES, N. R.; MOTA, C. C. S. da; CUNHA, C. A. M. da; ALENCAR, J. V. de; BRENNER, S.; LEAL, W. M. & BUFFARA, M. – Icterícia obstrutiva na blastomicose Sul Americana – apresentação de dois casos. An. Fac. Med. Univ. Paraná, 8: 25-39, 1965.

03. BARBOSA, W. – Blastomicose Sul-americana. Contribuição ao seu estudo no Estado de Goiás. Goiânia, 1968. Tese de Livre Docência.

04. BARBOSA, W.; DAHER, R. R. & OLIVEIRA, A. R. de – Formas linfático-abdominal da blastomicose sul-americana. Rev. Inst. Med. Trop. São Paulo, 10: 16-27, 1968.

05. BOCCALANDRO, I. & ALBUQUERQUE, F. J. M. – Icterícia e comprometimento hepático na blastomicose sul-americana. A propósito de 10 casos. Rev. Paul. Med. 56: 350-366, 1960.

06. BRITO, T. de; CASTRO, R. M. & SHIROMA, M. – Biopsia hepática na blastomicose sul-americana. Rev. Inst. Med. Trop. São Paulo, 10. 188-191, 1968.

07. CASTRO, R. M.; DEL NEGRO, G.; BASSOI, O. N. & FARIA, C. V. de – Dificuldades diagnósticas na blastomicose sul-americana. A propósito de oito casos. Rev. Paul. Med., 53: 479-496, 1958.

08. CUNHA, M. A. R. da; PEREIRA, A. A.; GOUVEIA, O. F. de; PIMENTEL, J. R. L.; SAAD, M.; TEIXEIRA, D. & MIYAHIRA, A. R. – Contribuição ao estudo radiológico da blastomicose sul-americana no aparelho digestivo. Hospital (Rio de Janeiro), 69: 169-174, 1966.

09. CUNHA MOTA, L. – Granulomatose paracoccidióidica ("Blastomicose Brasileira"). VI Intestino. An. Fac. Med. São Paulo, 21: 205-225, 1945.

10. DAHER, R. R.; VASCONCELOS, W. M. P. & CARDOSO, V. M. – Fígado e blastomicose sul-americana. J. Bras. Med. 25 83-90, 1973.

11. FAVA NETTO, C. – Contribuição para o estudo imunológico da blastomicose de Lutz. Rev. Inst. A. Lutz (S. Paulo), 21: 99-194, 1961.

12. FIALHO, F. – Localizações viscerais da micose de Lutz. Bol. Academia Nac. Med. ano 134 n. 1, 18-27, 1962.

13. FONSECA, L. C. & MIGNONE, C. – Paracoccidioidomicose do intestino delgado. Aspectos anátomo-clínicos e radiológicos. Rev. Hosp. Clin. Fac. Med. São Paulo, 31: 199-207, 1976.

14. FORATTINI, O. P. – Blastomicose da região pancreática. Rev. Paul. Med., 31: 165-172, 1947.

15. FRIOZZI, G. – O Fígado na blastomicose sul-americana. Arq. Hosp. S. Casa São Paulo, 7: 109-119, 1961.

16. MARTINEZ, R.; MENEGHELLI, U. G.; FIORILLO, A. M. & OLIVEIRA, R. B. de – O comprometimento gastrointestinal na blastomicose sul-americana (Paracoccidioidomicose). I. Estudo Clínico, radiológico e histopatológico. Rev. Ass. Med. Brasil, 25: 31-34, 1979.

17. MOSTO, D. & IARICI, V. – Presentation de un caso granuloma por Paracoccidioides brasiliensis. Rev. Ass. Med. Argent., 59: 826-830, 1945.