

PULMONARY MANIFESTATIONS IN THE INITIAL PHASE OF SCHISTOSOMIASIS MANSONI

Manoel Otávio C. ROCHA, Regina Lunardi ROCHA, Ênio Roberto P. PEDROSO, Dirceu B. GRECO, Cid Sérgio FERREIRA, José Roberto LAMBERTUCCI, Naftale KATZ, Roberto S. ROCHA, Dilermando F. REZENDE & Jayme NEVES.

SUMMARY

The clinical and radiological pulmonary manifestations in the initial phase of schistosomiasis mansoni were studied in thirty previously healthy individuals who were simultaneously infected. The findings were compared with those concerning a control group and related to possible pathogenetic factors.

The respiratory manifestations were of light or of moderate intensity, the dry cough being the most common symptom. The significant radiological alterations were: thickening of bronchial walls and beaded micronodulation, predominantly localized in the lower pulmonary fields.

It was observed significant association between wheezing and IgE levels, estimated by the area of immediate intradermal reaction, as well as between the number of blood eosinophils and the occurrence of radiological changes. Moreover, there was correlation between the worm burden and the presence of wheezing, thoracic pain and beaded micronodulation.

Thus, the clinical and radiological pulmonary manifestations described are significant part of the initial phase of schistosomiasis mansoni and present the worm burden, eosinophilia and levels of IgE as probable pathogenetic factors.

KEYWORDS: Schistosomiasis mansoni; Acute schistosomiasis; Lung disease, parasitic.

INTRODUCTION

The pulmonary manifestations in the early phase of schistosomiasis mansoni are worthy of a particular study in the general context of parasitosis, owing to the manifold aspects of their clinical features, radiological alterations and anatomopathological onset, besides its evolutive potential to serious pictures²³.

During the period of pulmonary migration of schistosomula, hemorrhages and inflammatory reactions, such as pneumonitis, endarteritis and arteriolitis, may occur. In the period following oviposition, the eggs retained in the pulmonary vessels bring about chronic inflammatory granulomatous reaction.

The respiratory symptomatology often occurs in the acute form, cough being its most common manifes-

tation^{7,24}. It can go unnoticed, however, if one is not aware of the problem from a clinical standpoint²³.

Though the pulmonary involvement has been described in acute schistosomiasis from the invasive period onward²⁴, the studies dealing systematically with the pulmonary manifestations in the early phases of the infection are few and old^{22,24}. Moreover, they have possibly been influenced by the large variety of factors such as the heterogeneity of the case history as far as the age group is concerned, nutritional condition, tobacco addiction or past history of bronchitis, previous infection by the parasite, among others. The study of radiological alterations in the thorax suffers mainly from the lack of a control group, which would enable

Medical School, Federal University of Minas Gerais, Postgraduate Course of Tropical Medicine, René Rachou Research Center (FIOCRUZ).

Correspondence to: Dr. Manoel Otávio C. Rocha. Faculdade de Medicina da UFMG. Av. Prof. Alfredo Balena 190, 30130-100 Belo Horizonte, MG, Brasil.

one to correlate them with the initial schistosomal infection more accurately.

This study aims at describing and discussing the clinical and radiological pulmonary alterations found in a homogeneous group of individuals acutely infected, comparing them with those observed in a control group as well as relating them to possible pathogenetic factors such as worm burden, blood eosinophilia and area of immediate intradermal reaction, taken as evaluation of IgE bound to mast cells.

PATIENTS AND METHODS

Two groups were studied: the first one, named infected group, constituted of thirty recruits belonging to the Fourth Communication Company of the Brazilian Army; the second one, the control group, composed of twenty-four recruits that served in the same Company in the following year.

All the individuals were males, eighteen and nineteen years old and agreed to participate in the present study voluntarily, receiving the information and treatment required in each case.

The patients of the first group were infected during military manoeuvres in Belo Horizonte, Minas Gerais, a notoriously endemic area for schistosomiasis. The diagnosis of the initial phase of the infection was based on the finding of eggs of *Schistosoma mansoni* in the stools, from fifty-seven to sixty days following the infectant bath, as well as on epidemic toxoinfectious picture and/or blood eosinophilia over 1000/mm³.

The individuals of the control group were healthy, showed the same percentage of tobacco addiction or past history of bronchitis as that of the other group. They all denied to have bathed previously in natural waters and/or presented negative intradermal antigen reaction for *S. mansoni*, and did not present either blood eosinophilia or presence of eggs of *S. mansoni* in two stool examinations.

The clinical evaluation consisted of a general clinical examination. The epidemiological condition of each patient and the possible clinical effects of the infection were especially tried to be characterized. Stress was laid on the manifestations of the respiratory apparatus.

The laboratorial study comprised a global specific hemogram (Leishman's staining method) and two parasitological stool examinations according to Kato-Katz method²⁰.

It was carried out intradermal reaction in the middle flexural part of the forearm by injecting 0.05 ml antigen of the adult worm containing 40 µgN/ml. The reading of the results was taken after fifteen minutes, the criterion for interpretation being the measure of the papular area, according to Pellegrino and Macedo's technique²⁶.

In the radiological study of the thorax, roentgen-photographies were utilized, by means of Movix 60/120 equipment, (Meditecnica, Brazil) and 70 mm film, developed by M5AN Kodak processing machine, in poste-

ro-anterior views. The findings were considered present when seen concurrently by at least two observers out of three, independently and at random.

Data Analysis

All the information was stored in a microcomputer by means of FOX PRO 2.0 database management system. The statistical analysis was carried out with the resources of the Epi-Info 5.01b software (USD Inc., Stone Mountain, GA) and the SAS for Windows program, version 6.08 (SAS Institute Inc.).

The original number of eggs passed in the stools was obtained by the arithmetic mean of the two counts. In the evaluation of the means and variances of the number of eggs eliminated in the faeces and the number of eosinophils in the peripheral blood the original numbers were square root transformed in order to reduce the asymmetrical distribution of the data. The means and variances of the area of immediate intradermal reaction were arrived at without any numeric transformation.

In order to make comparisons of two means, F test was used initially to verify the homogeneity of the populational variances. When it was proven that the variances were homogeneous, t test was done to compare the means. When the homogeneity of variance was not verified, Kruskal-Wallis' test was used.

In order to compare proportions, X² test with Yates correction and one-tailed Fischer's exact test were used. The relative risk was used as chance measure.

The predetermined level of statistical significance was 5%.

RESULTS

Most patients of the infected group (19 cases out of 30, corresponding to 63.3%) showed some respiratory sign or symptom of light or of moderate intensity. The clinical picture consisted mainly of dry cough (68.4% of the symptomatic cases) or productive cough (36.8% of the cases), further including the presence of wheezing in two patients without previous history of bronchial asthma and/or familial atopy, thoracic pain in two cases as well as dyspnoea on exertion and rhinorrhoea each in one case.

The vast majority of the infected patients (86.7% of the cases) presented some radiological pulmonary alteration possibly related to the schistosomal infection.

The predominantly significant radiological abnormalities in the infected group were the thickening of bronchial walls (66.7% of the acute cases, X² = 7.68; p=0.05) and beaded micronodulation (56.7%; X² = 11.62; p<0.01).

Although the scattered micronodulation occurred in 33% of the acute cases and only in 8.3% of the individuals of the control group, this difference was not statistically significant (X²=3.48; p=0.06). The retification and convexity of the medium arch as well as the promi-

TABLE 1

Pulmonary involvement in 30 patients in the initial phase of schistosomiasis mansoni: clinical and radiological manifestations and laboratory characteristics.

Case	Tobacco Addiction	Respiratory symptoms	Radiological Aspect	Area of IIT (cm ²)	Eosinophil count in peripheric blood (cells/mm ³)	Number of eggs per gramme of faeces
1	N	DC	MA rectified, BW thickened (RH base), MN (RH base)	1.45	2,464	36
2	N	PC	Normal	1.00	4,097	42
3	Y	A	MA rectified	1.20	1,334	12
4	Y	DC	MA convex, MN (RH and LH bases), rosary (LH base)	1.00	3,080	336
5	N	PC	MA rectified, BW hilar region (RH)	0.90	5,472	36
6	N	A	Normal	1.20	8,370	48
7	Y	A	MA slightly convex, BW and rosary (RH and LH bases), MN (RH base)	1.10	5,595	48
8	Y	A	Rosary (LH base)	1.20	3,019	30
9	N	A	BW (RH and LH base), macronodules (RH base), rosary LH, opacity (RH apex)	1.20	3,725	66
10	N	DC	MA rectified, PB (RH base), rosary (LH base)	1.00	131	66
11	N	W	MA slightly convex, BW (RH base), rosary (LH base)	2.05	5,060	222
12	Y	A	Normal	1.35	16,068	102
13	Y	DC	MA convex, BW and MN (RH base)	1.45	6,987	42
14	Y	DC	MA rectified	1.20	5,514	60
15	Y	A	BW (RH base)	1.00	4,510	6
16	N	A	MA slightly convex, BW (RH base), rosary (LH base)	1.20	6,049	102
17	N	DC	MA slightly convex, BW (RH base), rosary (LH base)	1.20	5,720	30
18	N	DC, CP, W	MA convex, BW (RH base), rosary (LH base)	3.30	1,023	378
19	N	A	MA convex, BW (RH base), rosary (LH base)	1.30	10,500	156
20	N	A	MA slightly convex, rosary (RH base)	3.30	1,327	246
21	Y	DC, PC, R	BW (RH base), rosary (LH base)	1.10	2,624	54
22	N	PC	BW (RH and LH bases), MN (LH base) prominent PA	0.80	5,928	60
23	N	DC, D	MA slightly convex, BW hilar region (RH), rosary (LH base)	0.70	3,088	439
24	N	DC	BW (LH base)	1.20	3,373	18
25	N	PC	BW (RH base)	1.00	2,300	156
26	N	DC	MA rectified, MN (LH base), rosary (RH and LH bases)	3.25	3,215	120

TABLE 1 (CONT.)

Pulmonary involvement in 30 patients in the initial phase of schistosomiasis mansoni: clinical and radiological manifestations and laboratory characteristics.

Case	Tobacco Addiction	Respiratory symptoms	Radiological Aspect	Area of IIT (cm ²)	Eosinophil counts in peripheric blood (cells/ mm ³)	Number of eggs per gramme of faeces
27	N	DC, PC	BW (RH base), MN (RH and LH bases), rosary (LH bases)	2.00	2,639	54
28	Y	DC, CP	MA convex, BW (RH base), rosary (LH base), prominent PA	0.70	8,618	462
29	N	DC	MA slightly convex, BW (RH base), MN(RH base), rosary (LH base)	1.10	4,520	90
30	N	A	MA convex, BW (RH base), MN (RH base)	0.90	6,003	36

IIT = immediate intradermic test

DC = dry cough

CP = chest pain

A = asymptomatic

PA = pulmonary artery

BW = bronchial wall

ex = examination

PC = productive cough

D = dyspnoea

Y = yes

RH = right hemithorax

LH = left hemithorax

MA = medium arch

W = wheezing

R = rhinorrhoea

N = no

MN = micronodules

Rosary = beaded MN

TABLE 2

Radiological and laboratory characteristics of 24 cases of control group

Cases	Tobacco Addiction	Respiratory Symptoms	Radiological aspects	Area of IIT (cm ²)	Eosinophil counts in peripheric blood (cells/mm ³)
1	Y	A	Normal	0.90	260
2	N	A	MA slightly convex, Rosary (LH bases)	0.50	0
3	N	A	MA slightly convex	0.90	123
4	N	A	Normal	0.90	780
5	N	A	MA slightly convex, BW and MN (RH and LH bases)	0.40	0
6	Y	A	Normal	0.30	292
7	Y	A	MA rectified, BW (RH and LH base)	0.60	649
8	Y	A	MA convex	0.40	348
9	Y	A	MA convex	0.40	540
10	N	A	MA slightly convex	0.60	272
11	N	A	Normal	1.00	180
12	Y	A	MA slightly convex	0.50	183
13	N	A	MA slightly convex, BW (LH base)	0.80	118
14	Y	A	MA rectified, BW (LH base)	0.50	71
15	N	A	MA convex, Rosary (LH base)	0.60	315
16	N	A	MA rectified	0.60	260
17	N	A	BW (RH base), MN (RH base), prominent PA	1.00	495
18	N	A	Normal	0.80	159
19	N	A	Normal	0.70	76
20	N	A	Normal	0.60	440
21	N	A	Normal	0.40	265
22	N	A	MA convex	0.50	504
23	N	A	Normal	0.50	245
24	Y	A	MA rectified, BW (LH base)	0.30	61

A = asymptomatic

Y = Yes

BW = Bronchial wall

MN = micronodules

IIT = immediate intradermic test

N = no

PA = pulmonary artery

Rosary = beaded MN

MA = medium arch

LH = left hemithorax

RH = right hemithorax

nence of the left pulmonary artery were equally found in the acute cases and in the controls. There was no statistically significant relation between the presence of clinical respiratory change and of radiological pulmonary abnormality.

TABLE 3

Clinical pulmonary manifestations presented by 30 patients in the initial phase of schistosomiasis mansoni.

CLINICAL MANIFESTATIONS	NUMBER OF PATIENTS	
	Absolute	%
Dry cough	13	43.3
Productive cough	7	23.3
Chest pain	2	6.6
Wheezing	2	6.6
Dyspnoea	1	3.3
Rhinorrhoea	1	3.3

There was no correlation between the area of intradermal reaction and the clinical respiratory alterations in the infected group, when these changes were analysed as a whole. Nevertheless, when each respiratory manifestation was studied specifically, correlation between wheezing and the area of intradermal reaction ($p=0.006$) was verified. On the other hand, no connexion between the latter and the global or the specific radiological pulmonary alterations could be established.

The occurrence of clinical pulmonary changes, taken together, was not associated with the number of the peripheric blood eosinophils. Neither was there correlation between the level of blood eosinophilia, the presence of wheezing and other clinical respiratory manifestations when individually analysed. In the infected group, however, significant association between the level of blood eosinophilia and the occurrence of radiological pulmonary changes as a whole was detected ($p=0.016$). The same relation was not observed when each radiological pulmonary alteration was studied separately (thickening of bronchial walls, beaded or spread micronodulation).

The worm burden, assessed by the number of eggs excreted in the faeces, was significantly associated with the presence of wheezing ($p=0.028$) and the occurrence of thoracic pain ($p=0.002$). Moreover, correlation between the worm burden and the presence of beaded micronodulation was ascertained ($X^2=8.36$; $p=0.004$). It was not observed association of the worm burden either with the clinical respiratory alterations, taken as a whole, or with the radiological pulmonary changes, whether they were global or specific.

Tobacco addiction was related neither with the respiratory symptomatology of the infected group nor with the radiological pulmonary alterations verified in both the infected and the control groups.

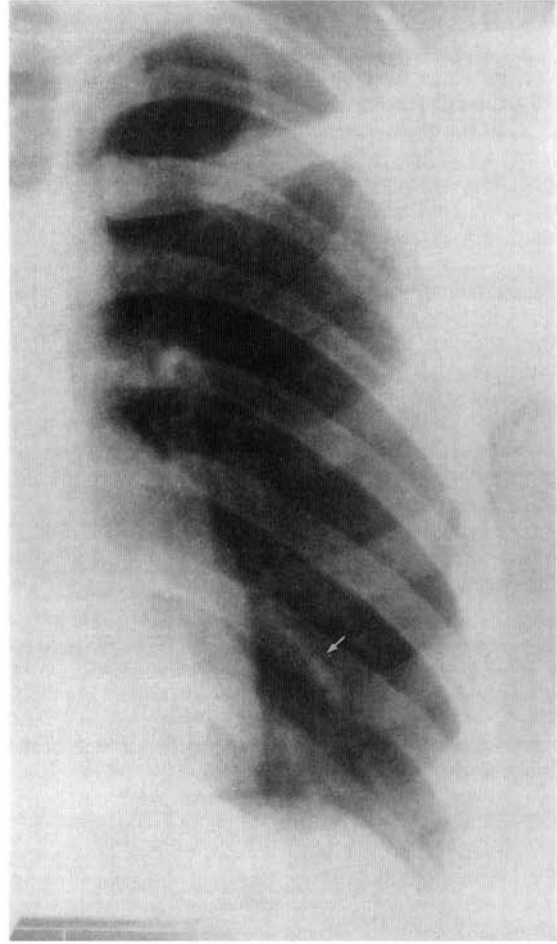


Fig. 1 - Acute schistosomiasis mansoni. Beaded micronodulation (arrow).

DISCUSSION

The clinical and radiological manifestations in the initial phase of schistosomiasis mansoni presumably translate not well-known physiopathogenetic mechanisms, which are possibly related to histopathologic alterations due to the passage of the worms through the lungs and also related with the host defense reactions against the presence of the worms, their eggs and output. At the root of these alterations, it has been considered the influence of different factors such as the global and tetrine reactivity of the infected host, worm burden, immunologic reactions of various kind owing to the presence of worms and their eggs, as well as the mechanic alterations brought about by the passage of schistosomula through the lungs, among others^{7,15,24}.

According to GELFAND¹², the pulmonary lesions of the acute phase would probably be caused by the worms and not by the eggs. Others¹⁵ think that the clinical and radiological pulmonary manifestations may not

depend on the local presence of the worms and/or their eggs, being possibly due to the deposition of immuno-complexes, activation of the complement system and migration of leukocytes and macrophages.

In our case history, 63.3% of the patients presented some respiratory sign or symptom. This high incidence coincides with what has been observed by some authors^{7,14}, contradicting, nevertheless, the experience of others^{10,22}.

Similarly to our observation, in the literature consulted, cough was the most frequent symptom, especially of the dry sort^{4,7}. Productive cough, thoracic wheezing, dyspnoea on exertion, thoracic pain and rhinorrhoea are described in literature in percentages resembling those recorded in our cases^{22,24,30}.

The clinical respiratory manifestations were light or mild. This finding corresponds to the fact that the pulmonary histopathological alterations during the initial phase of the disease are generally unimportant²⁷.

Radiological pulmonary alterations were identified in the vast majority of the infected patients (86.7% of the cases), similarly to other authors' observations^{22,24}, especially the thickening of bronchial walls, the beaded and the scattered micronodulation. The thickening of bronchial walls, detected in 66.7% of the patients of the infected group, seems to correspond in part with the increase of the normal pulmonary striation reported by some authors²⁴, as well as with the reinforcement of the bronchovascular texture observed by others^{7,22}.

In 56.7% of the cases, micronodulation with pararterial linear disposition could be detected radiologically, giving rise to the "rosary" appearance described in the chronic phase of schistosomiasis⁹. Another important finding was the micronodulation scattered in the pulmonary bases, in 33% of the patients. Similar alterations were reported by MAINZER²². Though often observed by some researchers^{22,24}, the hilar alterations were not a significant finding in our case history. Only two of these cases presented prominent pulmonary artery standing out from the cardiac shadow.

The alterations of the medium arch of the cardiac shadow, regarded as radiological expression of pulmonary hypertension by some authors³⁰, were not significantly predominant in the infected group, in relation to the control group. From our standpoint, these alterations are frequently found in young patients submitted to radiological thoracic study. The absence of significant differences in their prevalence in either of the groups studied has not enabled us to relate them to the acute infections process.

The absence of statistically significant association between the respiratory symptomatology and the radiological alterations coincides with other author's observations^{22,24}.

In schistosomiasis mansoni, as well as in other helminthic infections, large quantities of IgE are produced¹⁸. It has been suggested that IgE would be involved in the defense against helminthic infections, on

the contrary of what occurs in allergies, in which this immunoglobulin produces disease¹⁶.

In Gell and Coombs' hypersensitivity reaction (type 1), which are primarily mediated by IgE, this immunoglobulin is bound to mast cells by its Fc extremities and, by reacting with the allergen, elicits a complex series of reactions ending in cellular degranulation and release of mediators capable of provoking bronchoconstriction and attracting eosinophils^{3,18}.

HUSSAIN et al¹⁷ verified significant correlation between the area of immediate intradermal test, following intradermal injection of adult worm antigen of *S.mansoni*, and serum levels of IgE, detected by radioimmunoassay, in 35 individuals with schistosomal infection existing for less than a year. Thus, the intradermal reaction constitutes a simple method which enables the detection of IgE bound to mast cells and a rough evaluation of the serum levels of parasite-specific IgE.

Eosinophilia, as well as the increase of IgE, is a hallmark of acute schistosomiasis mansoni. The specific eosinophil granules contain lysosomal hydrolases, cationic proteins such as the major basic protein - MBP¹⁴, eosinophil cationic protein (ECP) and eosinophil-derived neurotoxin (EDN), besides peroxidase³².

MBP is toxic for schistomula, but this action is nonselective, since mammalian cells can be damaged, too^{4,13}. ECP and peroxidase are also toxic for helminths and mammalian cells^{1,19}. The pathogenetic action of eosinophils can be evinced indirectly by the extracellular localization of MBP, which is suggestive of the occurrence of cellular degranulation¹⁰. Elevated serum levels of MBP have been found in patients with eosinophilia from various causes, the correlation between eosinophilia and the levels of MBP being confirmed³¹. Significantly elevated levels of MBP were observed in asthmatic patients' sputum⁸. Furthermore, eosinophils are capable of releasing histamine from mast cells of rats and human basophils²⁵. On observing the absence of correlation between blood eosinophilia and the respiratory manifestations, considered either together or separately, it must be taken into account the fact that these cells are of predominantly parenchymatous localization. The number of cells observed in the peripheric blood may not adequately express their concentration in the lungs.

This work verified significant association between the area of immediate intradermal reaction, taken as an approximate evaluation of parasite-specific IgE and the occurrence of wheezing ($p=0.006$). This finding might corroborate previous impressions of occurrence of hypersensitivity reaction in the initial phase of schistosomiasis mansoni⁷. Nevertheless, the small number of patients should be taken into account.

The worm burden, as well as the host response, seems to have significant influence on the morbidity of schistosomiasis mansoni. Generally speaking, the several authors who have reported association between

the morbidity and intensity of the schistosomal infection, studied the chronic phase of the disease and utilized the number of eggs eliminated in the faeces as expressions of the worm burden^{2,6,21}. This association - eggs in the faeces and worm burden - was demonstrated in humans, postmortem, in the chronic phase of the infection⁵, and, in the initial phase, in an experimental study²⁹, in which the relation between the intensity of the infection and morbidity was also verified. More recently, it was verified significant though not very strong connexion between the worm burden and morbidity in patients in the initial phase of schistosomiasis mansoni (ROCHA et al., 1995).

In our study, the worm burden, expressed by the number of eggs excreted in the faeces, was significantly associated with the presence of wheezing, thoracic pain and beaded micronodulation. All this strengthens the impression that the intensity of the infection is a determining factor of morbidity, also during the initial phase of human schistosomal infection.

The absence of significant connexion between tobacco addiction and clinical respiratory manifestations or radiological pulmonary changes, together with the utilization of the control group, epidemiological history and laboratorial results, enable us to affirm that both the clinical and the radiological picture are integral part of a wider process, of acute epidemic toxoinfectious kind and of schistosomal nature.

RESUMO

Alterações pulmonares da fase inicial da esquistossomose mansoni

Foram estudadas as alterações clínicas e radiológicas pulmonares da fase inicial da esquistossomose mansoni em 30 indivíduos previamente saudáveis, que se infectaram simultaneamente. Os achados foram comparados aos de um grupo - controle e relacionados a possíveis fatores patogênicos como carga parasitária, eosinofilia sanguínea e área de reação intradérmica imediata, esta como estimativa de IgE ligada a mastócito. As manifestações pulmonares foram de intensidade leve ou moderada, sendo a tosse seca o sintoma mais comum. As alterações radiológicas significativas constaram de espessamento de paredes brônquicas, micronodulação em rosário e micronodulação esparsa, localizadas predominantemente nas porções inferiores dos campos pulmonares.

Verificou-se associação significativa de sibilos e área da reação intradérmica imediata, bem como entre o número de eosinófilos sanguíneos e a ocorrência de alterações radiológicas tomadas em conjunto. Houve correlação entre a carga parasitária, expressa pelo número de ovos eliminados nas fezes, e a presença de sibilos, dor torácica e micronodulação em rosário.

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