Original Article

Differences in the clinical and radiological presentation of intrathoracic tuberculosis in the presence or absence of HIV infection*

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Abstract

Objective: To describe the differences in the clinical and radiological presentation of tuberculosis in the presence or absence of HIV infection. **Methods:** A sample of 231 consecutive adults with active pulmonary tuberculosis admitted to a tuberculosis hospital were studied, assessing HIV infection, AIDS, and associated factors, as well as re-evaluating chest X-rays. **Results:** There were 113 HIV-positive patients (49%) Comparing the 113 HIV-positive patients (49%) to the 118 HIV-negative patients (51%), the former presented a higher frequency of atypical pulmonary tuberculosis (pulmonary lesions accompanied by intrathoracic lymph node enlargement), hematogenous tuberculosis, and pulmonary tuberculosis accompanied by superficial lymph node enlargement, as well as presenting less pulmonary cavitation. The same was found when HIV-positive patients with AIDS were compared to those without AIDS. There were no differences between the HIV-positive patients without AIDS and the HIV-negative patients. Median CD4 counts were lower in HIV-positive patients with intrathoracic lymph node enlargement and pulmonary lesions than in the HIV-positive patients with pulmonary lesions only (47 *vs.* 266 cells/mm^3; $p < 0.0001$), in HIV-positive patients with AIDS than in those without AIDS (136 *vs.* 398 cells/mm^3; $p < 0.0001$) and in patients with atypical pulmonary tuberculosis than in those with other forms of tuberculosis (31 *vs.* 258 cells/mm^3; $p < 0.01$). **Conclusion:** Atypical forms and disseminated disease predominate among patients with advanced immunosuppression. In regions where TB prevalence is high, the presence of atypical pulmonary tuberculosis or pulmonary tuberculosis accompanied by superficial lymph node enlargement should be considered an AIDS-defining condition.

Keywords: Tuberculosis, pulmonary; HIV infections; Radiography, thoracic.

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Introduction

The epidemic of acquired immunodeficiency syndrome (AIDS) has caused changes in the clinical and radiological presentation of tuberculosis (TB) in adults, as described at the beginning of the 1980s.[1] In HIV-infected (HIV-positive) patients, atypical intrathoracic forms (non-cavitated perihilar pulmonary infiltrates or pulmonary infiltrates in the middle and lower thirds of the lungs accompanied by hilar or mediastinal lymph node enlargement, resembling the lesions seen in primary TB) appeared, and cases of hematogenous TB, TB at multiple sites, and pulmonary TB with normal chest X-rays became common.[1-9]

The differences found in the presentation of TB in HIV-positive patients are due to cellular immunodeficiency secondary to the progressive destruction of CD4 lymphocytes by HIV,[4,6,9,10] and the tuberculous lesions can result from the reactivation of old foci or from re-infection.[4,6,8] Therefore, CD4 counts in peripheral blood are used to evaluate the immunological status of patients infected with the virus, and the counts thus obtained can be correlated with the clinical and radiological presentation of TB.[3,6-12] When TB manifests in HIV-positive patients with relatively preserved immunity (CD4 > 350 cells/mm^3), the clinical and radiological presentation is similar to that seen in individuals who are not infected with HIV (HIV-negative individuals).[6] In patients with low CD4 counts, especially lower than 200 cell/mm^3, TB can have an atypical presentation.[3,6-11]

The objective of the present study was to describe the differences in the clinical and radiological presentation of intrathoracic TB in HIV-positive and HIV-negative patients, as well as to determine the correlation between CD4 lymphocyte counts and the presence of atypical forms of TB in HIV-positive patients living in an area of high prevalence of TB/HIV co-infection.

Methods

This was a cross-sectional study involving a sample of 231 consecutive patients admitted to the Rio Grande do Sul Department of Health *Hospital Sanatório Partenon*, located in Porto Alegre, Brazil, between 1997 and 2001. The following inclusion criteria were applied: being 15 years of age or older; never having been treated for TB; presenting positive sputum smear microscopy; having undergone HIV testing; and having undergone simple anteroposterior and lateral chest X-ray.

The data were obtained through the re-evaluation of chest X-rays and the review of medical charts. The variables analyzed were as follows: age; gender; alcoholism; use of illicit drugs; corticosteroid use; duration of symptoms; presence of multifocal disease, diabetes mellitus, neoplasias, and opportunistic diseases; results of HIV testing; number of CD4 T lymphocytes; and radiological findings.

Sputum smear microscopy was performed using the Ziehl-Neelsen technique. The HIV testing was performed using the ELISA method, and positive results were confirmed by Western blot. The CD4 counts were obtained using flow cytometry. Alcoholism and drug addiction were considered present when they had been registered on the medical chart by the treatment team. Multifocal disease was defined by the presence of superficial lymph node enlargement in patients with pulmonary TB.

The chest X-rays were independently evaluated by two radiologists, who had no knowledge of the results of HIV testing, in order to identify the types of TB; the location of the lesions in the lung segments; and the presence of cavitary lesions, hilar or mediastinal lymph node enlargement, and pleural effusion. In case of inconsistency between the evaluations, the chest X-rays were jointly examined and, in the event of the inconsistency persisting, a third radiologist was consulted so that a consensus could be reached. The types of TB were characterized using the following classification:

1) Classic pulmonary TB: pulmonary lesions unaccompanied by hilar or mediastinal lymph node enlargement;
2) Tuberculous pneumonia: homogeneous consolidation with air bronchograms, with or without intrathoracic lymph node enlargement;
3) Hematogenous TB: diffuse pulmonary infiltrate with or without intrathoracic lymph node enlargement;
4) Tuberculoma: nodular lesion without intrathoracic lymph node enlargement;
5) Mediastinal lymph node TB: intrathoracic lymph node enlargement as a single lesion;
6) Atypical pulmonary TB: non-cavitated foci of consolidation located in the perihilar region

or in the anterior segment of the upper lobe and in the basal segments of the lower and middle lobes or of the lingula, accompanied by intrathoracic lymph node enlargement;
7) Pleural TB: pleural effusion without pulmonary or mediastinal lesions; and
8) Pulmonary TB with normal chest X-ray.

For the purpose of this study, the patients infected with HIV who presented associated opportunistic diseases, such as pneumocystosis, cerebral toxoplasmosis, esophageal candidiasis, cryptococcosis, histoplasmosis, cytomegalovirus infection, or Kaposi's sarcoma, were considered to have AIDS.

The results are presented as mean and standard deviation or percentage of patients with a given characteristic. Non-normally distributed data (CD4 and duration of symptoms) were normalized by logarithmic transformation, for the purpose of analysis, and are presented as median and minimum and maximum values. The analysis was carried out using the chi-square test, Fisher's exact test, and the Student's t-test. Values of $p < 0.05$ were considered significant.

Since the study used secondary data obtained by the review of medical charts, there was no interference with the patients or with the treatment routine. The permission to use the information was granted by the hospital facility based on the safeguards ensuring data confidentiality and patient privacy.

Results

Of the 231 patients included in the study, 69.7% were male, 60.6% were Caucasian, 59.7% were alcoholics, and 36.2% were illicit drug users. The mean age was 37.7 ± 12.9 years. The delay between the onset of symptoms and the diagnosis ranged from 10 to 540 days (median, 60 days) and was longer than 90 days in 48% of the patients. Diabetes mellitus was identified in 4.3% of the cases and multifocal disease in 13%. None of the patients used corticosteroids or had neoplasia. A total of 113 patients (48.9%) tested positive for HIV.

There were no differences between the HIV-positive and the HIV-negative patients in terms of gender, race, alcoholism, or presence of diabetes mellitus (Table 1), nor were any differences observed in terms of duration of symptoms: 60 days (range, 10-360 days) *and* 90 days (range, 14-540 days), respectively ($p = 0.284$). However, the HIV-positive patients were younger (34.3 ± 9.3 *vs.* 41.1 ± 15 years; $p < 0.0001$), used illicit drugs more frequently, and more often presented multifocal disease in comparison with the HIV-negative patients (Table 1).

Table 1 - Distribution of demographic, clinical, and radiological variables by HIV test results.

Variable		Total	HIV+		HIV–		p
			n	%	n	%	
Gender	Male	161	80	70.8	81	68.6	0.722
	Female	70	33	29.2	37	31.4	
Race	Caucasian	140	68	60.2	72	61.0	0.896
	Non-Caucasian	91	45	39.8	46	39.0	
Alcoholism[a]	Yes	138	66	64.7	72	62.6	0.749
	No	79	36	35.3	43	37.4	
Use of illicit drugs[b]	Yes	79	65	61.3	14	12.5	<0.0001
	No	139	41	38.7	98	87.5	
Multifocal disease	Yes	30	27	23.9	3	2.5	<0.0001
	No	201	86	76.1	115	97.5	
Diabetes mellitus	Yes	10	2	1.8	8	6.8	0.103
	No	221	111	98.2	110	93.2	
Intrathoracic lymph node enlargement	Yes	24	23	20.4	1	0.8	<0.0001
	No	207	90	79.6	117	99.2	
Pulmonary cavitation	Yes	188	80	70.8	108	91.5	<0.0001
	No	43	33	29.2	10	8.5	
Pleural effusion	Yes	38	21	18.6	17	14.4	0.392
	No	193	92	81.4	101	85.6	

[a]No information available for 14 patients (11 HIV+; 3 HIV–); and [b]no information available for 13 patients (7 HIV+; 6 HIV–).

The comparison between the HIV-positive and the HIV-negative patients revealed that the former presented a significantly higher frequency of pulmonary lesions accompanied by intrathoracic lymph node enlargement, as well as presenting less pulmonary cavitation, and that there was no difference in terms of pleural effusion accompanied by pulmonary lesions (Table 1). Of the 23 HIV-positive patients with intrathoracic lymph node enlargement, 16 were classified as having atypical pulmonary TB, 5 were classified as having hematogenous TB, and 2 were classified as having tuberculous pneumonia. The only HIV-negative patient with lymph node enlargement had hematogenous TB.

In terms of the types of TB, the distribution was different in the HIV-positive and in the HIV-negative patients ($p < 0.001$) (Figure 1). Atypical pulmonary TB occurred only in the HIV-positive patients, who also presented higher frequencies of hematogenous TB and tuberculous pneumonia and, consequently, a lower frequency of classic pulmonary TB. There were no cases of mediastinal lymph node TB, pleural TB, or TB with normal chest X-ray.

Of the 113 HIV-positive patients, 79 (99.9%) were classified as having AIDS. Of those, only 16 (20.3%) used antiretroviral drugs, all of them using those drugs irregularly and for no more than 90 days. The patients with AIDS differed from the HIV-positive patients without AIDS by presenting a higher frequency of multifocal disease and of intrathoracic lymph node enlargement accompanied by pulmonary lesions, as well as by presenting less pulmonary cavitation (Table 2). These patients also differed in terms of the distribution of the types of TB ($p < 0.0001$) (Figure 2). Of the 16 cases of atypical pulmonary TB, 15 occurred among the patients with AIDS.

The HIV-positive patients without AIDS differed from the HIV-negative patients only by being younger (36.4 ± 10.5 *vs.* 41.1 ± 15 years; $p = 0.045$) and by using illicit drugs more frequently (60.6 *vs.* 12.5%; $p < 0.0001$). There were no differences between these two groups in terms of the other demographic, clinical, or radiological characteristics (Tables 1 and 2; Figures 1 and 2).

In the present study, CD4 counts were measured in 57 HIV-positive patients and ranged from 3 to 1288 cells/mm^3 (median, 195 cells/mm$^{3)}$. The counts were lower in the patients with mediastinal lymph node enlargement accompanied by pulmonary lesions - 47 cells/mm^3 (range, 3-268 cells/mm^3) - than in those with pulmonary lesions only - 266 cells/mm^3 (range, 7-1288 cells/mm^3) ($p < 0.0001$). The CD4 counts were also lower in the patients with AIDS - 136 cells/mm^3 (range, 3-1288 cells/mm^3) - than in the HIV-positive patients without AIDS - 398 cells/mm^3 (range, 272-689 cells/mm^3) ($p < 0.0001$). Median CD4 counts by type of TB, which were lower in the patients with atypical pulmonary TB - 31 cells/mm^3 (range, 3-71 cells/mm^3) - than in those with any of the other types ($p < 0.01$), are shown in Figure 3. A total of 30 patients had CD4 counts 200 cells/mm^3, and 27 had counts > 200 cells/mm^3. The group with CD4 counts ≤ 200 differed from the group with CD4 counts > 200 by presenting a higher frequency of intrathoracic lymph node enlargement (50 *vs.* 3.7%; $p = 0.0001$) and less pulmonary cavitation (53.3 *vs.* 85.2%; $p = 0.010$).

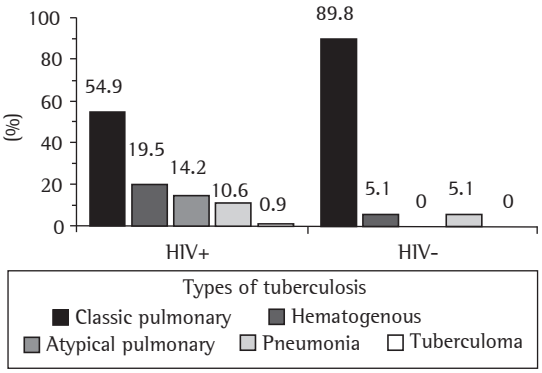

Figure 1 - Frequency of the types of tuberculosis in adults with positive sputum smear microscopy by results of HIV testing.

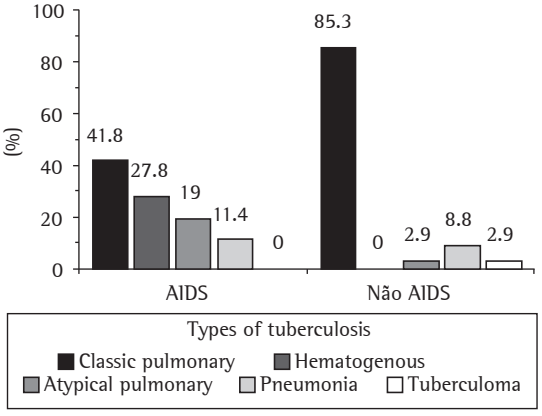

Figure 2 - Frequency of the types of tuberculosis in adults with positive sputum smear microscopy by the presence or absence of AIDS.

Table 2 - Distribution of demographic, clinical, and radiological variables by the presence or absence of AIDS in HIV-positive patients.

Variable		Total	With AIDS		Without AIDS		p
			n	%	n	%	
Gender	Male	80	54	68.4	26	76.5	0.384
	Female	33	25	31.7	8	23.5	
Race	Caucasian	68	49	62.0	19	55.9	0.541
	Non-Caucasian	45	30	38.0	15	44.1	
Alcoholism[a]	Yes	66	42	60.9	24	72.7	0.241
	No	36	27	39.1	9	27.3	
Use of illicit drugs[b]	Yes	65	45	61.6	20	60.6	0.919
	No	41	28	38.4	13	39.4	
Multifocal disease	Yes	27	27	34.2	0	0.0	<0.0001
	No	86	52	65.8	34	100.0	
Diabetes mellitus	Yes	2	0	0.0	2	5.9	0.089
	No	111	79	100.0	32	94.1	
Intrathoracic lymph node enlargement	Yes	23	22	27.8	1	2.9	0.003
	No	90	57	72.2	33	97.1	
Pulmonary cavitation	Yes	80	50	63.3	30	88.2	0.007
	No	33	29	36.7	4	11.8	
Pleural effusion	Yes	21	16	20.3	5	14.7	0.487
	No	92	63	79.7	29	85.3	

[a]No information available for 11 patients (10 with AIDS; 1 without AIDS); and [b]no information available for 7 patients (6 with AIDS; 1 without AIDS).

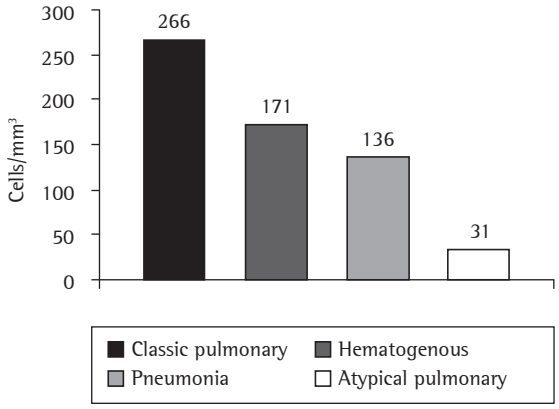

Figure 3 - Median CD4 counts by the types of tuberculosis.

Multifocal disease occurred in 30 patients, 27 of whom (23.9%) were HIV-positive, and 3 of whom (2.5%) were HIV-negative ($p < 0.0001$). All of the HIV-patients with multifocal disease also presented other opportunistic diseases. In 63.2% of the 17 patients with multifocal disease whose CD4 counts were measured, the counts were ≤ 200 cells/mm^3.

Discussion

Some studies in the literature report higher frequencies of intrathoracic lymph node enlargement accompanied by pulmonary lesions in HIV-positive patients (mean of 23.3%) than in HIV-negative patients (mean of 8.9%).[2-5,11,13-16] In studies in which the differences between the two groups were not significant, this may have occurred due to the lower level of immunosuppression of the HIV-patients included or to the lower prevalence of co-infection in the population studied.[11,16] The high frequencies of lymph node enlargement in HIV-negative patients found in some studies, and which are higher than those observed in the present study,[3-5,15] can be explained by the occurrence of primary TB in countries of low TB prevalence or by racial factors, since lymph node enlargement is more common in Blacks, which could explain the higher rates found in some studies conducted in Africa and in Haiti.[3-5,15] In the present study, the HIV-patients with lymph node enlargement and pulmonary lesions had lower CD4 counts than did those with pulmonary lesions only -47 cells/mm^3 (range, 3-268 cells/mm^3) *vs.* 266 cells/mm^3 (range, 7-1288 cells/mm^3) - similarly to what was observed in another study -45 cells/

mm³ (range, 18-245 cells/mm³) *vs.* 299 cells/mm³ (range, 34-644 cells/mm³).[3] Intrathoracic lymph node enlargement was more common in the patients with AIDS than in the HIV-positive patients without AIDS (27.2 *vs.* 2.9%), as well as being more common in the HIV-positive patients with CD4 counts ≤ 200 cells/mm³ than in those with CD4 counts > 200 cells/mm³ (50 *vs.* 3.7%). Higher prevalences of lymph node enlargement in HIV-positive patients with lower CD4 counts have also been found in other studies.[6,8,9,11] Therefore, intrathoracic lymph node enlargement in adults with pulmonary TB strongly suggests the presence of severe immunosuppression. This has also been observed in studies recently conducted in Brazil.[17,18]

The cases of atypical pulmonary TB in the present study occurred only in HIV-positive adults with low CD4 counts - 31 cells/mm³ (range, 3-71 cells/mm³) - similar to what has been observed in the literature.[3,6,8,9] In such patients, the HIV-induced impairment of cellular immunity allows the development of pulmonary infiltrates in any region of the lung, typically without cavitations but accompanied by intrathoracic lymph node enlargement. This finding is in accordance with those of studies that have found atypical forms in immunosuppressed patients.[1-4,6-9,11-13,18-20] This form of presentation can be considered a true case of primary TB in areas of low TB prevalence, where the primary infection can occur later in adults.[21,22] However, in Brazil, it is more likely that it is a case of post-primary TB by endogenous reactivation or by recent re-infection in a patient with immunodeficiency.

Hematogenous TB was also more prevalent in the HIV-positive patients, especially in those with a higher level of immunosuppression, than in the HIV-negative patients. High frequencies of this severe form of TB in HIV-positive patients have been identified in several studies.[1,3,8,13,15,16,20] However, among those that compared HIV-positive and HIV-negative patients, the difference in the frequency of hematogenous TB was significant only in the series with the greatest number of cases studied,[15] which is in accordance with what has been observed in a study conducted in Brazil.[16]

Tuberculous pneumonia, despite having had a similar frequency in the HIV-positive and in the HIV-negative patients, was twice as prevalent in the patients with AIDS as in the HIV-negative patients. This type of TB is not typically described in the literature as a separate entity. Some authors classify the TB cases that manifest in the form of homogeneous consolidation in a lobe or segment in adults as being primary TB, whereas others consider such cases to be post-primary TB. However, such cases could represent the lung involvement after the aspiration of caseating material from a ganglion of progressive primary TB or from a ganglion in which there was a reactivation of old foci (post-primary TB).[23] Since it has been observed that the frequency of intrathoracic lymph node involvement caused by TB is higher in HIV-positive patients than in HIV-negative patients, it is expected that the number of cases of this type of TB will increase.

In the present study, the lower frequency of classic pulmonary TB observed in the HIV-positive patients (as compared to the HIV-negative patients - 54.9 *vs.* 89.8%), in the patients with AIDS (as compared to the HIV-positive patients without AIDS - 41.8 *vs.* 85.3%), and in the patients with CD4 ≤ 200 cells/mm³ (as compared to those with higher CD4 counts - 26.7 *vs.* 70.4%) was due to the high number of cases of hematogenous TB and of atypical pulmonary TB in these patients.

The lower frequency of pulmonary cavitation found in the HIV-positive patients than in the HIV-negative patients, associated with the level of immunosuppression, is in accordance with what has been reported in the literature.[2-5,13,15,16,19,24] This frequency was lower in the patients with AIDS than in the HIV-positive patients without AIDS (63.3 *vs.* 88.2%) and in the patients with CD4 counts ≤ 200 cells/mm³ than in those with CD4 counts > 200 cells/mm³ (53.3 *vs.* 85.2%). A study conducted in Africa found cavitation in 56.2% of the patients with CD4 counts < 200 cells/mm³ and in 79.1% of the patients with CD4 counts ≥ 200 cells/mm³.[24] Other studies have found lower values: 28.9% and 15.4% in patients with CD4 counts < 200 cells/mm³; and 53% and 66.7% in those with CD4 counts > 200 cells/mm³.[8,11] The high rate of cavitation found in the patients evaluated in the present study, both in the HIV-positive (70.8%) and in the HIV-negative (91.5%) patients, is partly due to the delay in diagnosing TB, since they were patients with a long duration of symptoms prior to hospitalization. A study that evaluated patients with a prolonged duration of symptoms (an average of 127 days in the HIV-positive patients and of 143 days in the HIV-negative patients) showed high rates

of cavitation in the two groups (59.3 and 71.7%, respectively).[14] In addition to delayed diagnosis, it is possible that, in areas of high TB prevalence, HIV-positive patients develop the disease in a phase in which their cellular immunity is relatively intact (prior to developing AIDS), and, therefore, present cavitation.[4,6,9] This hypothesis is consistent with experimental data that indicate that cavity formation requires a strong lymphocyte reactivity to the *Mycobacterium tuberculosis* antigens.[25]

The presence of superficial lymph node enlargement accompanied by pulmonary TB was more frequent in the HIV-positive patients (23.9%) than in the HIV-negative patients (2.5%). A studied conducted in the northeast of Brazil has shown this association in 16.7% of the HIV-positive patients.[26] Assuming that the lymph node involvement is due to TB, this defines the occurrence of disease in more than one foci, which is a situation that rarely occurred prior to the advent of AIDS, since TB in adults was characterized as a unifocal disease. A study that defined disseminated disease as the presence of lesions in two or more noncontiguous extrapulmonary organs (typically in lymph nodes) revealed that disseminated TB was more common in HIV-positive patients without AIDS than in HIV-negative patients (28 *vs.* 6%; $p < 0.01$).[3] The authors of the present study prefer to use the term multifocal TB to designate the forms of the disease in more than one noncontiguous site when secondary to simultaneous evolution of foci established during previous lymphohematogenous dissemination. The term disseminated is reserved for TB cases with diffuse pulmonary infiltrate (hematogenous TB), with or without foci in other organs. The term miliary TB corresponds to cases of hematogenous TB with diffuse micronodular pulmonary infiltrate on chest X-ray. In the present study, we observed that the HIV-patients with multifocal disease presented a higher frequency of hematogenous TB and atypical pulmonary TB, as well as presenting less pulmonary cavitation, than did those without multifocal disease, which indicates that this form of TB presentation correlates with the presence of immunosuppression.

The comparison between the HIV-positive patients without AIDS and the HIV-negative patients revealed no differences between the two groups in terms of frequency of intrathoracic lymph node enlargement accompanied by pulmonary lesions, frequency of cavitation, frequency of multifocal disease, or distribution of the types of TB. These findings differ from those obtained in a study in which the HIV-positive patients without AIDS presented a higher frequency of intrathoracic lymph node enlargement and of disease in more than one organ, as well as presenting less pulmonary cavitation, than did the HIV-negative patients, although the mean CD4 counts in the HIV-positive patients - 133 cells/mm^3 (range, 11-677 cells/mm^3) - were similar to those obtained in the present study - 136 cells/mm^3 (range, 3-1288 cells/mm^3).[3] The explanation for this apparent contradiction is that HIV-positive patients who live in areas of high TB prevalence, as is the case of the area where the present study was conducted, acquire TB earlier, when their immunity is still preserved, and develop typical forms of the disease.[4] In view of this, in such areas, only HIV-positive patients with atypical pulmonary TB (atypical radiological profiles being predictors of CD4 counts < 200 cells/mm^3)[7] or with multifocal disease should be considered to have AIDS. This is in accordance with a study conducted in Africa,[24] in which it was concluded that the value of a simple diagnosis of pulmonary TB for predicting the level of immunity in HIV-positive patients is limited since the disease develops in a broad spectrum of CD4 counts, and is in accordance with the criteria for definition of AIDS cases used in Brazil.[27]

The introduction of the highly active antiretroviral therapy (HAART) has reduced AIDS-related morbidity and mortality.[28] Among HIV-positive patients, the use of HAART has decreased the incidence of TB and increased CD4 counts.[29] Therefore, it is expected that TB will again manifest in its classic form in patients with AIDS who are under appropriate treatment with HAART, which was not the case of the patients evaluated in the present study. A study that evaluated the radiological presentation in co-infected patients using and not using HAART[30] revealed that the former group more often presented a profile typical of post-primary TB, which is consistent with the restoration of CD4 counts through antiretroviral therapy.

The data from the present study, which showed that the presentation of TB in the patients with AIDS is different from that seen in HIV-negative patients, suggest that the presence of HIV infection in patients with atypical pulmonary TB or with TB accompanied by palpable superficial lymph node enlargement must be investigated, and that every

HIV-positive patient with these forms of presentation of TB should be considered to have AIDS.

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