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RESPIRATORY COMPLICATIONS IN BRAZILIAN PATIENTS INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS

Adriana WEINBERG (1) & Maria Irma Seixas DUARTE (2).

SUMMARY

Purpose: To determine how often and by what means an indentifiable pulmonary pathogen can be recognized in human immunodeficiency virus (HIV) infected patients with respiratory disorders in Brazil, which are the most frequently observed microorganisms and what impact specific therapy has on these agents.

Patients and Methods: Thirty-five HIV seropositive subjects with respiratory complaints were studied. All patients had a complete history, physical examination and blood counts.

The pulmonary assessment included chest radiograms; sputum examination for bacterial and fungal pathogens; bronchoscopy with bronchoalveolar lavage and transbronchial biopsy. Patients with treatable complications received standard antimicrobial therapy.

Results: One or more microorganisms were found in 24 subjects and another 3 individuals showed nonspecific interstitial pneumonitis. The sputum examination identified the pulmonary pathogens in 7 cases. The bronchoalveolar lavage and the histopathologic examination were diagnostic in 14% and 83%, respectively, of the 28 individuals that were submitted to bronchoscopy. The most frequently identified microorganism was *P. carinii* (55%), followed by M. tuberculosis (41%) and cytomegalovirus (8%). The clinical, laboratory and radiographic findings failed to distinguish the specific pulmonary pathogens. Twenty-three individuals with **P. carinii** pneumonitis and/or tuberculosis received specific therapy; among the evaluable patients the therapeutic response rates were 79% for PCP and 100% for TB.

Conclusions: We have determined that tuberculosis, **P. carinii** and cytomegalovirus pneumonitis are the most common respiratory opportunistic diseases in Brazilian patients infected with HIV. The histologic evaluation was crucial in order to identify the pulmonary pathogens. Tuberculosis in AIDS individuals displayed clinical and radiographic findings atypical for reactivation disease. However, most of the features observed in HIV infected patients had been previously described in infection of the normal host. Furthermore, the AIDS subjects showed a good therapeutic response to anti-tuberculous drugs.

KEY WORDS: AIDS; HIV infection; Respiratory disorders; Tuberculosis; **Pneumocystis carinii** pneumonia; CMV pneumonitis; Nonspecific interstitial pneumonitis.

INTRODUCTION

Pulmonary infection is the most commonly recognized presenting manifestation and life-threatening complication in patients with acquired immunodeficiency syndrome (AIDS).

The respiratory diseases are ultimately related to the pathogenicity of the human immunodeficiency virus (HIV), which causes AIDS alone or potentiated by cofactors. The virus determines severe immunosuppression by destruction and functional alteration of CD4+ T lymphocytes, furthered by B lymphocyte and macrophage func-

(1) Department of Infectious Diseases of the "Hospital das Clínicas" of the University of São Paulo School of Medicine and Laboratory of Virology, Institute of Tropical Medicine, São Paulo, Brazil.
(2) Department of Pathology of the University of São Paulo School of Medicine. São Paulo, Brazil.
Address for correspondence: Adriana Weinberg, M.D., University Hospital School of Medicine, Campus Box C227, 4200 East Ninth Avenue, Denver, Colorado 80262,U.S.A.

tional abnormalities. Thus, the agents of the respiratory infections will reflect the failure of these immunologic defenses, particularly of the cell mediated immunity. However, the frequency of each microorganism will also depend on the background prevalence of infection with these pathogens in the local population. In North America, the most frequently encountered agent is *Pneumocystis carinii* which will ultimately infect 80% of the individuals with AIDS [26]. Other causes of dyspnea, cough, or radiologic abnormalities include mycobacteria, cytomegalovirus, fungi, Kaposi sarcoma, pyogenic bacteria and nonspecific interstitial pneumonitis, of yet unclear etiology [24,36]. There is a dearth of data on the incidence of lung infections or neoplasias in AIDS patients from third world countries. This information, however, is very important for designing AIDS health projects in these areas. Furthermore, the spectrum of opportunistic diseases in the third world countries might also indicate future trends of AIDS associated infections in low income populations of developed countries.

The goal of the present study was to determine how often and by what means an identifiable pulmonary pathogen can be recognized in HIV infected patients with respiratory disorders in Brazil, which are the most frequently encountered microorganisms and what impact specific therapy has on these agents.

PATIENTS AND METHODS

Study Population

All of the 35 HIV seropositive adults admitted with respiratory complaints at the Infectious Diseases Ward of the Hospital of the Clinics of the University of São Paulo Medical School between June 1988 and May 1989 were studied. All the subjects required pulmonary investigation because of fever, dyspnea or coughing and abnormal chest radiographs. Fifteen individuals were also candidates for an inhalatory pentamidine protocol and were followed prospectively. The data on the remaining 20 patients were obtained from chart review.

The evaluation of each patient included a complete history, physical examination, chest radiographs, complete blood counts and erythrocyte sedimentation rates and/or mucoprotein dosage as nonspecific indicators of inflammatory activity. Anemia was considered to occur when hemoglobin levels were below 120g/l; leukopenia was defined as less than $5x10^9$ white blood cells/l; lymphopenia as less than $8x10^8$ lymphocytes/l; and thrombocytopenia, platelets below $150x10^9$/l. Quantilation of CD4+ T lymphocytes was not available. Delayed type hypersensitivity was evaluated with 2 units of PPD, candida, trychophyton and streptococcal varidase antigens. Anergy was diagnosed when the patient failed to react to any of these antigens.

Diagnostic Procedures

Sputum induced by 20 to 30 min 3% saline inhalation was examined for bacterial and fungal pathogens by standard procedures, represented by direct staining (Gram, Ziehl Neelsen, potassium hydroxide and toluidine blue O) and the appropriate cultures.

Whenever the primary investigation did not yield a positive result or if the patient's clinical condition was worsening in the presence of specific therapy the individual was submitted to fiberoptic bronchoscopy which included bronchoalveolar lavage (BAL) and transbronchial biopsy. Tissue specimens were not obtained in the patients with bleeding diathesis or in the presence of severe bronchospasm.

The material obtained by BAL was submitted to viral culture, by inoculation onto human foreskin fibroblast monolayers, and to fungal and bacterial investigation as described for the sputum. The tissue fragments were used for histopathologic examination.

Histologic studies. Biopsy specimens of the lungs were formaldehyde fixed, stained with hematoxilin-eosin, Grocott's methenamine silver and Ziehl Neelsen techniques. Special emphasis was placed on the identification of inflammatory lesions, invasive fungi, mycobacteria and cells containing viral inclusions. The following characteristics of tissue injury were individually scored on a scale 0 to 3: bronchial hyperplasia, metaplasia, dysplasia, inflammation and fibrosis; alveolar exudate, edema, hyaline membrane formation, presence of macrophages, hemorrhage, necrosis, type 2 pneumocytes hyperplasia and bronchial metaplasia; interstitial edema, congestion, inflammatory infiltrates, necrosis and fibrosis.

Pneumocystis carinii pneumonia (PCP) was

indicated by the presence of at least one cluster of cysts on the toluidine blue O smear of sputum or BAL or on the Grocott's tissue stain.

Mycobacterial pneumonia was defined by the encounter of acid fast bacili in the sputum, BAL or biopsy specimens, with or without granulomas, or by culture. When biochemical identification of the mycobacterial species was not available, tuberculosis (TB) was diagnosed based on the finding of a positive PPD and/or when there was a prompt therapeutic response to anti-tuberculous drugs.

The diagnosis of cytomegalovirus pneumonia relied on the encounter of typical intranuclear inclusion bodies in areas of lung inflammation and or positive cultures.

Nonspecific interstitial pneumonitis was characterized by diffuse alveolar damage of varying degrees associated with increased numbers of macrophages and lymphocytes and absence of microbial pathogens in the sputum, BAL or biopsy specimens.

A nondiagnostic procedure was defined by the absence of microbial pathogens on sputum or BAL examinations and the lack of adequate tissue specimens for histologic studies.

Therapy

Pathogens identified by the above techniques were treated as follows: *P. carinii* - oral or intravenous trimethoprim (TMP), 20 mg/kg/day with sulfamethoxazole (SMX) 100 mg/kg/day, or intravenous or inhaled pentamidine 300 to 600 mg/day; tuberculosis - isoniazid (INH) 400 mg/day, rifampin (RPM) 600 mg/day and pyrazinamide (PZA) 20 to 30 mg/kg/day. Patients with PCP and severe pulmonary failure also received 40 mg of methylprednisolone 3 times a day for 7 days [20]. Ganciclovir was not available for cytomegalovirus therapy.

RESULTS

Characteristics of the Study Population

Thirty-five consecutive HIV positive adults with respiratory complaints were evaluated in this study. As shown in Table 1 the subjects consisted of 32 males and 3 females with a mean age of

Table 1
Demographic characteristics of the study population.

Age	34.11 (22 to 52)
	n° of patients
Sex	
males	32 (91%)
females	3 (9%)
Ethnicity	
white	26 (74%)
black	7 (20%)
Asian	2 (6%)
Risk factors	
homosexual/bisexuals	21 (60%)
drug users	8 (23%)
contact with prostitutes	2 (6%)
blood transfusion	1 (2%)
unknown	3 (9%)

Table 2
Nonrespiratory infections and neoplasms in 35 HIV seropositive adults.

Diagnosis	Cases
Candidiasis	20
oro-esophageal	20
Tuberculosis	7
lymphadenitis	3
miliary	2
cutaneous	1
pericarditis	1
Viral infections	7
cytomegalovirus chorioretinitis	2
cytomegalovirus colitis or enteritis	2
genital Herpes simplex	3
cutaneous zoster	1
Bacterial sepsis	3
Staphylococcus aureus	2
Salmonella enteritidis	1
Kaposi sarcoma	6
Diarrhea	11
cytomegalovirus colitis or enteritis	2
Giardia lamblia	3
Isospora belli	1
Strongyloides stercoralis	1
lymphoma	1
no pathogens	6
Central nervous system infections	6
Toxoplasma gondii	4
Cryptococcus neoformans	2
Pseudomonas aeruginosa	1

Table 3
Diagnostic findings in 27 HIV seropositive patients with respiratory disorders.

Diagnosis	N°	Radiologic findings				Diagnostic specimen		
	of case	Diffuse interst infiltrates	Focal	Cavitary lesions	Effusion	Sputum	BAL	Biopsy
PCP	11	8	3			6		5
PCP+TB	3	2		1			1	2
PCP+CMV	1	1					1	1
TB	8	2	4	1	1	1	1	6
CMV	1	1						1
NIP	3	2	1					3

34.11 years and range of 22 to 52 years. There were 26 white patients, 6 black and 2 Asian ones. The risk factors for HIV acquisition were the following: 21 males related homosexual or bisexual activities, 3 females and 5 males were intravenous drug users, 2 male patients reported frequent contacts with prostitutes, 1 subject had a blood transfusion history and the remaining 3 patients denied any known risk factors.

Thirty-two individuals were characterized as AIDS cases according to the CDC 1987 surveillance criteria [33]. The remaining 3 patients related moderate weight loss, 1 had oral moniliasis and persistent diarrhea caused by Giardia lamblia. In 22 instances the diagnosis of AIDS relied on the encounter of opportunistic infections (presented in detail in table 2) associated or not to wasting syndrome, 3 patients had isolated wasting syndrome, 5 patients presented with Kaposi sarcoma associated to opportunistic infections, 1 had Kaposi sarcoma alone and another patient had a non Hodgkin lymphoma . Of the 35 individuals, only 1 AIDS patient was receiving zidovudine, 200 mg 6 times daily.

Among the 35 subjects, 7 (20%) had a specific microorganism identified in the sputum and 28 required bronchoscopic examination, which was successful in recognizing the cause of the respiratory disorder in 20 cases (71%). The BAL evaluation alone was diagnostic in 4 of the 28 patients submitted to bronchoscopy (14%) and the histologic examination in 19 of the 23 cases in which a biopsy was obtained (83%). In 8 patients the pulmonary investigation failed to determine a diagnosis of the respiratory process. All these subjects underwent bronchoscopy, but in 5 cases a transbronchial biopsy was not obtained, in 2 patients the tissue fragments were inadequate and in the last case the histopathologic exam showed normal lungs. At the time when the bronchoscopy was performed, 4 of these 8 patients were receiving TMP-SMX and 1 subject was taking INH, RPM and PZA, empirically. We report the data on the remaining 27 individuals in whom a pulmonary diagnosis was recognized.

Pneumocystis carinii pneumonia

Table 3 shows that the most frequently identified pulmonary pathogen was *P.carinii*, which was found either alone (11 cases) or in combination with other infectious agents (3 with TB and 1 with CMV) in 55% of the patients.

The chest radiograms of 12 subjects showed diffuse interstitial infiltrates and in 3 cases there were localized consolidations. One patient, who had TB associated to PCP displayed small cavitations interspersed with coarse pulmonary infiltrates.

The diagnosis of PCP was established by the encouter of the pathogen in the sputum of 6 individuals, in the BAL of 2 subjects and only on tissue axamination in 7 cases. Of the 9 patients submitted to bronchoscopy, 4 were receiving SMP-TMX for 2 to 10 days by the time when the diagnostic procedure was performed and in these individuals *P. carinii* was found exclusively on histopathologic exam. Another 2 subjects, who had been previously suspected of suffering from PCP, were receiving prophylactic dapsone and fansidar, respectively, at the time of diagnosis. In these patients the *P.carinii* were observed on sputum evaluation.

In 10 cases (67%), the PCP alone or associated to other infectious agents identified in this study

was the presenting symptom of AIDS. Overall there was a 3±5 months interval between AIDS diagnosis and study admission for individuals with PCP. However, the patients displayed several features of advanced HIV disease: 55% had pronounced weight loss (6.1±6.8 kg), 100% had anergy, 73% showed anemia, 27% leukopenia, 90% lymphopenia and 36% thrombocytopenia. Furthermore, all the subjects had augmented sedimentation rates and/or mucoproteins.

Of the 15 patients identified with PCP, 9 received TMP-SMX as primary therapy and 6 inhalatory pentamidine. One patient on TMP-SMX developed a significant rash and was switched to intravenous pentamidine. Two other individuals failed to respond to TMP-SMX, but pentamidine was not available for them. Of the 6 subjects initially treated with pentamidine, 2 were switched to TMP-SMX, because of profound neutropenia in 1 case and treatment failure in another one. However, the last patient did not respond to TMP-SMX either.

There were 4 deaths caused by pulmonary insufficiency among the 15 patients with PCP. Of these, 1 subject, who had PCP associated to TB, had less than 72 hours of specific therapy. Thus, the PCP related mortality was 21% in this study.

Tuberculosis

This was the second most frequent diagnosis in our series, established in 41% of the patients (11 out of 27). Tuberculosis was present alone in 8 individuals and associated to PCP in 3 cases.

Chest roentgenograms showed localized interstitial and nodular infiltrates in 4 cases, diffuse interstitial or miliary lesions in 5 subjects, including the 3 patients who had TB and PCP and an isolated effusion in 1 individual. Furthermore, 2 patients had pleural effusions associated with parenchymal infiltrates and 1 individual displayed a pericardial effusion. Cavities were seen in 2 cases, but in 1 of them the lesions were atypical inasmuch as they were small and scattered throughout both lungs (this patient had PCP too).

The diagnosis was obtained by smears for acid fast bacilli (AFB) in the sputum of 1 patient and in the BAL of 2 subjects. In 8 cases, only the histopathologic exam was diagnostic, including 2 individuals who had been receiving INH, RMP and PZA at the time when the fiberoptic bronchoscopy was performed. The histologic evaluation of the specimens obtained from the AFB positive subjects showed typical granulomas in 6 out of 10 cases. In 1 of the remaining 4 biopsies, the pathogenic agents were found inside alveolar macrophages accompanied by alveolitis, interstitial edema and congestion. In the remaining 3 cases the AFB were observed in the middle of necrotic areas, surrounded by mononuclear inflammatory infiltrates. In 2 of these last 3 patients the AFB positive lesions were located in the bronchial walls and in one of them corresponded to a bronchoscopically identified endobronchial mass. Two of the patients with atypical histologic changes (endobronchial mass and AFB inside alveolar macrophages) had their AFB isolated in culture and identified as M. tuberculosis. Another 2 patients were known to have positive PPD. In 1 case the hypersensitivity was still present at diagnosis. However, in the other one, it had become negative at the beginning of the pulmonary disease.

Ten out of the 11 TB patients met the CDC criteria for AIDS: 6 of them had other opportunistic diseases (previous or concomitant PCP in 5 cases, cerebral toxoplasmosis in 2 and 1 Kaposi sarcoma) and 7 had extrapulmonary lesions (lymphadenitis in 3 cases, miliary with liver infection in 2, cutaneous 1 and pericarditis 1). The remaining individual had oral candidiasis, intestinal giardiasis, a 3 kg weight loss in 3 weeks, anemia, lymphopenia, elevated erythrocyte sedimentation rate and mucoproteins. His clinical condition was similar to the TB patients that had been diagnosed as AIDS 2.6±6.3 months before admission (8 out of 11 patients, 73%, had their AIDS condition recognized during the study) and who also showed weight loss in 87% of the cases (mean of 7.1±6.9 kg), anergy in 80%, anemia in 87%, leukopenia in 37%, lymphopenia in 62%, thrombocytopenia in 25% and elevated sedimentation rates and mucoproteins in 100%. The clinical and laboratory abnormalities observed in the TB patients were comparable to those noted in the individuals with PCP.

All the patients received INH, RMP and PZA after the TB was recognized and a favorable response was observed in 9 subjects. The remaining 2 patients died at 24 and 48 hours, respectively, after the specific therapy was started and could not be evaluated from the standpoint of the therapeutic response. Of note, 1 of these 2 subjects had TB

associated to PCP and developed severe pulmonary insufficiency. The other patient had miliary TB. However, the cause of death was neurologic and related to HIV central nervous system pathology, as evidenced at postmortem examination. Two individuals had transaminase elevations during therapy, but none of them required drug discontinuation. In conclusion, all the TB patients, in this series, who received more than 72 hours of specific treatment showed clinical and laboratory improvement and good tolerance to anti-tuberculous drugs.

Cytomegalovirus Pneumonitis

Of the 27 HIV seropositive patients with an identified pulmonary disorder, 2 (8%) had CMV pneumonitis. The CMV infection occurred as an isolated event in 1 subject and associated with PCP in the other. Both individuals had fever, cough, moderate dyspnea and diffuse interstitial infiltrates on chest radiographs. They had been receiving TMP-SMX for 3 and 10 days, respectively, without improvement, at the time the bronchoscopy was performed. In both cases the histologic evaluation disclosed CMV pneumonitis characterized by frequent viral inclusions in the alveolar epithelium surrounded by necrosis and inflammatory infiltrates. CMV was not isolated from the BAL, but was recovered in culture from other organs.

Both patients had disseminated CMV infection, including intestinal lesions in both cases and adrenal insufficiency in one subject. Furthemore, the 2 individuals exhibited severe weight loss (20 kg), anergy, anemia and lymphopenia. One of them had leukopenia and the other one thrombocytopenia.

The patients did not receive anti-CMV specific treatment. One died during the hospital admission of intestinal hemorrhage and the other one was discharged in poor, but stable conditions.

Nonspecific Interstitial Pneumonitis

In 3 patients (11%) NIP was characterized on histology. The 3 subjects had fever and mild pulmonary symptoms. Their chest radiograms showed diffuse interstitial infiltrates in 2 cases and localized nodular lesions in the remaining subject. Only 1 individual had AIDS, defined by the occurrence of cerebral toxoplasmosis. The AIDS patient reported modest weight loss; 1 subject with AIDS related complex who was tested showed maintained delayed type hypersensitivity; all the individuals had anemia, 2 had leukopenia, 1 had thrombocytopenia and 1 lymphopenia. All the patients survived and were discharged in stable conditions.

DISCUSSION

This study documents the prevalence of pulmonary pathogens in Brazilian HIV seropositive patients admitted with respiratory symptoms. After thorough investigation, a diagnosis was established in 27 individuals, 24 of whom (89%) had at least one infectious agent. The most frequently observed microorganism was *P. carinii* (55%) , followed by M. tuberculosis (41%) and cytomegalovirus (8%).

The importance of the diagnostic evaluation is emphasized by the high incidence of opportunistic infections and the good therapeutic response of most of them. Since clinical and radiographic characteristics could not distinguish between PCP and TB, the most frequent respiratory complications in our patients, the identification of the infectious agent was critical for establishing the correct diagnosis. More recently, seric LDH elevations were associated with PCP [25]. Of note, the sputum examinations had an unexpectedly low yield for both *P.carinii* and M.tuberculosis, 40 and 10%, respectively. AFB have been identified in the sputum at rates similar with ours or more frequently [28,38]. However, with regard to PCP, many studies have shown much better results either with sputum induction [2,9,30] (55 to 79% sensivity) or BAL [5,9,17] (approximately 90% diagnostic power compared to 22% in our study). The use of better techniques such as small particle inhalator, sputum liquefaction [42], monoclonal antibodies [35] and more experience with bronchoalveolar washings may improve our results. However, it is interesting to observe that many patients in our study were already on TMP-SMX, INH, RMP and PZA or other antibiotcs by the time the bronchoscopy was performed. In the 6 cases where the empiric treatment was ascertained, only the histologic examination was diagnostic. Overall, the transbronchial biopsy was the diagnostic tool in 83% of the subjects, emphasizing the importance of this procedure.

Of the opportunistic diseases studied here, tuberculosis deserves special attention. Early AIDS studies showed that less than 1% of pulmonary

infections were caused by M. tuberculosis [24]. More recent surveys, however, found TB in 2% of AIDS cases in San Francisco [10], 5% in New York[8], 10% in Florida [7] and 21% at a university hospital in New Jersey [38]. An association between tuberculosis and HIV infection was shown in intravenous drug users, Haitians, black and Hispanic individuals and might cause important public health problems in prisons and other environments that include these patients [4, 29, 35]. In our series, M. tuberculosis was responsible for 41% of the pulmonary diseases of HIV seropositive patients, equally distributed among all the races and risk categories (data not shown) These findings are in accordance with previous necropsy studies in Brazilian AIDS patients that observed a TB incidence of 20% [21]. The high frequency of tuberculosis in Brazilian HIV infected individuals reflects the equally increased incidence of M. tuberculosis in the general population of our country (1988 coefficient= 57.3/100,000 habitants, National Division of Sanitary Pneumology). Similar observations were done in Africa, too [1]. Although cultures were not available for all the mycobacteria identified in this study, they were all considered M. tuberculosis because the clinical findings and therapeutic responses were more consistent with TB than with M. avium-intracellulare infection. Atypical mycobacteria are known to cause disseminated disease in 25 to 50% of AIDS patients, commonly associated with wasting syndrome, general malaise and rarely affecting the lungs[16,41]. In contrast, our patients had predominant respiratory symptoms, accompanied by abnormal chest radiograms. Among the 11 TB patients, only one showed typical upper lobe cavities on the roentgenograms. In the remaining cases, the chest radiographs suggested tuberculosis because of miliary or interstitial infiltrates and pleural or pericardial effusions in accordance with Spanish studies [6], but in contrast to reports from regions of low TB prevalence [31]. Furthermore, only 10% of the patients had positive sputum examinations, which was consistent with the predominance of interstitial and serosal lesions. It is interesting to note that 4 out of 11 patients had serosal lesions, which are considered suggestive of primary TB. However, a study that specifically addressed this question in intravenous drug users from New York determined that most of the cases of tuberculosis in AIDS patients represent reactivations [35]. Our findings indicate that in high TB prevalence areas primary infections might be equally important as reactivations. Conversely, secondary TB lesions in AIDS patients might assume clinical and radiographic features predominantly seen in primary tuberculosis of the normal host.

Histopathologic evaluation of the TB patients showed typical granulomas in 60% of the cases, comparable with prevoius reports [11]. In the remaining lung specimens, there were AFB either surrounded by conspicuous areas of necrosis or with little inflammatory reaction. This finding is not surprising, because HIV infected patients have deficient cell mediated immune mechanisms. It is also supported by the small number of subjects who exhibit a positive tuberculin reaction: 9% with 2 units of PPD in our study, 39% with 5 units of PPD reported by others [10]. Moreover, the lack of a competent immune system allows for dissemination of the disease, emphasized by the identification of extrapulmonary lesions in 64% of our TB patients and in 70 to 82% of the cases reported elsewhere[10,12].

It is important to note that only extrapulmonary TB and positive HIV serology are defined as AIDS by the Centers for Disease Control [33]. Although the numbers are very small and further studies will be necessary to draw definitive conclusions, we did not observe any significant clinical or laboratory difference between the HIV seropositives with TB who met the CDC AIDS criteria and the one who did not, suggesting that lung tuberculosis by itself might indicate the presence of full-blown immunodeficiency and hence AIDS. It has also been implied that M. tuberculosis infections could be present at an early stage of the HIV associated immunosuppression and predate the diagnosis of AIDS [29]. In our study, however, a comparison of the clinical and laboratory data, as well as time from AIDS diagnosis between TB and PCP patients showed similar results, suggesting that the subjects affected by these two opportunistic diseases were at similar stages of HIV infection.

As tuberculosis becomes a growing problem among HIV infected individuals, both in developed and third world countries, more interest is placed on the questions regarding therapeutic responses. In our series, 9 patients who survived for the first few days after diagnosis and received INH, RPM and PZA showed satisfactory clinical improvement. This is in agreement with most previous reports [3,6,10,29] but it may not be true for all the manifestations of the disease, since apparently

neurotuberculosis might progress despite appropriate therapy [3]. Although minor side effects were noted in 2 individuals, none of our patients required therapy discontinuation.

Infection with *P. carinii* was as common in our AIDS subjects as it has been determined for the North American ones [26,31]. Considering the individuals who had a definite AIDS diagnosis, 62% (15 out of 24) had PCP too. This is higher than the figures reported for Brazilian AIDS patients by either empirical diagnosis [12] or necropsy studies [21], (29% and 13%, respectively), which underscores the importance of a thorough diagnostic investigation. The clinical and radiographic spectrum of the PCP observed in this study was also similar to previous reports, including fever, cough and dyspnea and either diffuse interstitial lesions, or localized consolidations on chest X-ray films [19,22]. One patient with TB and PCP had small cavities associated with diffuse infiltrates. With regard to the therapeutic response, the number of patients enrolled in our study was too small to allow for significant conclusions, other than both aerosol pentamidine and TMP-SMX seemed to be effective in approximately 80% of the individuals, which is in accordance with the rest of the literature [13,15,18,23,34,40].

There appears to be an extremely high prevalence of cytomegalovirus in patients with AIDS, both in developed and third world countries [32,39]. In this study, CMV was observed in 8% of the lung infections. Although the pathogenic role of the CMV and hence the diagnostic value of its encounter in the lungs in AIDS related respiratory disorders has been questioned [14], in our patients, the presence of active inflammation around the cells that bore viral inclusions indicate that the CMV was contributing to the pulmonary disease. However, none of the cytomegalovirus lung infections were fatal, despite of the lack of specific therapy. These findings suggest that CMV can be a true pulmonary pathogen in AIDS patients, but the viral disease might not be rapidly progressive.

It is important to recognize that in 11% of the HIV seropositives with biopsy proven lung inflammation no pathogen could be identified. The numbers were even greater in other series, where nonspecific interstitial pneumonitis accounted for 32% of the episodes of clinical pulmonary disease in AIDS patients [36]. The cause of NIP has not yet been established, but there is some evidence that HIV might be directly involved, since patients who were taking zidovudine apparently had less nonspecific interstitial pneumonitis than untreated individuals [27]. In our study, NIP was identified more frequently in subjects who lacked evidence of opportunistic infections at any site. Although these findings might support a direct role of HIV in the genesis of NIP, other putative agents, such as Epstein Barr virus [36] or HTLV I [37], could not be excluded.

The spectrum of respiratory diseases in this study differs from the North American series in various aspects including the lack of Kaposi sarcoma and other neoplasias. The diagnosis of these disorders is rarely established by bronchoscopic procedures and usually requires open lung biopsies, which could not be performed in our patients [24].

In conclusion, by means of a thorough diagnostic investigation including histologic evaluation, we have determined that tuberculosis, *P.carinii* and cytomegalovirus pneumonitis are the most common respiratory opportunistic diseases in Brazilian patients infected by HIV. The clinical and radiographic findings of AIDS subjects with tuberculosis, although not typical of reactivation disease, displayed most of the characteristics previously described in infection of the normal host. Furthermore, the patients showed a good therapeutic response to anti-tuberculous drugs.

RESUMO

Complicações respiratórias em pacientes brasileiros infectados pelo vírus da imunodeficiência humana.

Objetivo: Determinar a frequência e os meios pelos quais é possivel identificar um agente patogênico respiratório em pacientes brasileiros infectados pelo vírus da imunodeficiência humana (HIV); quais são os microorganismos mais comuns; e qual é o impacto da terapêutica específica.

Pacientes e Métodos: Trinta e cinco pacientes HIV positivos, com queixas respiratórias foram estudados. Todos os pacientes tiveram história, exame físico e testes hematólogicos. A avaliação da patologia respiratória incluiu radiografia pulmonar, exame do escarro para bactérias e fungos, broncoscopia com lavagem bronquiolo-alveolar e

biopsia transbronquica. Pacientes com patologias tratáveis receberam a terapêutica indicada.

Resultados: Um ou mais organismos foram encontrados em 24 pacientes, e outros 3 pacientes mostraram pneumonite intersticial inespecífica. O exame de escarro identificou o agente patogênico pulmonar em 7 casos. O lavado bronquiolo-alveolar e o exame histopatológico definiram o diagnóstico em 14% e 83%, respectivamente, entre os 28 pacientes que foram submetidos à broncoscopia. O organismo mais comun foi *P.carinii* (55%), seguido por M.tuberculosis (41%), e citomegalovírus (8%). Os achados clínicos, laboratoriais e radiológicos não discriminaram os agentes patogênicos. Vinte e três pacientes com PCP ou tuberculose receberam terapêutica específica; entre os pacientes que puderam ser avaliados o tratamento foi bem sucedido em 79% dos episódios de PCP e 100% em TB.

Conclusões: Determinamos que TB, PCP e CMV são as causas mais frequentes de infecções respiratórias em pacientes brasileiros infectados pelo HIV. O exame histológico foi essencial para firmar o diagnóstico etiológico. A TB em pacientes aidéticos assumiu formas semelhantes à TB primária em pacientes imunocompetentes e apresentou boa resposta terapêutica.

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