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Histopathological Analysis about Autopsies from HIV/AIDS Patients—About Two Decades of Research Comparing Results before and after Antiretroviral Therapy Advent

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ABSTRACT

Objectives: This study considers 489 autopsies of HIV/AIDS patients who died from acute respiratory failure and describes the demographic data, etiology, and histological pulmonary findings of HIV associated diseases, comparing results before and after introduction of antiretroviral therapy. Methods: The following data were obtained: age, sex, and major associated diseases (found at the autopsy). Pulmonary histopathology was categorized as: diffuse alveolar damage; pulmonary edema; alveolar hemorrhage; and acute interstitial pneumonia. Odds ratio of the HIV/AIDS-associated diseases developing a specific histopathological pattern was determined by logistic regression. Results: A total of 355 men were studied. The mean age was 37 years old. Bronchopneumonia presented in 43% and Pneumocystis jiroveci pneumonia in 38% of patients. Pulmonary histopathology showed diffuse alveolar damage in 31% and acute interstitial pneumonia in 23%. The multivariate analysis showed a significant and positive association between diffuse alveolar damage with disseminated tuberculosis, cirrhosis and sepsis; and acute interstitial pneumonia with Pneumocystis jiroveci pneumonia and cytomegalovirosis. After the introduction of antiretroviral therapy we observed an increase in the prevalence of bacterial bronchopneumonia, sepsis and cirrhosis; and a decrease in Pneumocystis jiroveci pneumonia and cytomegalovirosis. Conclusions: Coherent to literature, this study showed a decrease of respiratory failure mortality associated with some opportunistic infections after antiretroviral therapy introduction. But an increased prevalence of sepsis, bronchopneumonia and sepsis was observed too. The most prevalent pulmonary histopathological pattern was diffuse alveolar damage, which suggested a positive association with disseminated tuberculosis, sepsis and cirrhosis.

Keywords: AIDS; Acute Respiratory Failure; Pathology

1. Introduction

The lungs have been the most frequent organs involved with AIDS-associated diseases leading to death. Acute respiratory failure (ARF) is the leading reason for intensive care unit (ICU) admission and the main cause of death of HIV-infected patients, mainly because of severe infectious diseases, like broncopneumonia and *Pneumocystis jiroveci*pneumonia (PJP) [1-8].

Many studies report changes in the causes of ARF after the introduction of combination antiretroviral therapy (ART) [3,6,9], with a great impact on therapeutic of HIV-infected patients. But there is little recent information about pulmonary pathology associated with these changes and HIV-related diseases at autopsies.

Based on information above, we performed a retrospective study about 489 autopsies of patients with HIV/AIDS whose cause of death was ARF in order to better describe the demographic data and etiological and histological pulmonary findings for different HIV/AIDS-associated pathologies comparing before and after introduction of ART.

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2. Material and Methods

2.1. Autopsies

The present study was carried out at a tertiary complex center. From 1990 to 2008, 26,560 medical autopsies were performed. ARF was the main cause of death in 4710 (17.7%) of patients. From these, the diagnosis of HIV/AIDS was made in 489 cases (10.4%), who were included in the study.

We performed a systemic review including all microscopic and macroscopic diagnosis of death at autopsy, and all medical records of the patients included.

All clinical and *postmortem* data from patients enrolled in this study were collected with legal permission, after informed consent was obtained from a family member and after the approval of the Internal Review Boards. We excluded patients younger than one year of age, those without ARF and/or without HIV/AIDS.

We also obtained data regarding each patient's age, sex, and major underlying associated diseases (as determined at autopsy).

Pulmonary histopathological analyses were performed in all HIV-infected cases. After a complete review, the most prevalent histopathological findings were categorized as:

1) Diffuse alveolar damage (DAD): diffuse involvement and uniform temporal appearance of alveolar collapse, hyaline membranes, obliterative fibrosis, neo-septa formation, and moderately organizing fibrosis

2) Pulmonary edema (PE): accumulation of proteinaceous fluid in the alveolar spaces, giving the appearance of a granular, pink coagulate within such spaces

3) Alveolar hemorrhage (AH): presence of blood in the alveolar spaces

4) Acute interstitial pneumonia (AIP): widened and edematous alveolar septa, usually accompanied by mononuclear inflammatory infiltrate of lymphocytes, histiocytes, plasma cells, and neutrophils.

All lungs were analyzed by microscopy even when medical records indicated the patient's diagnosis. For at least four weeks, the lungs were fixed in 10% formalin prepared in 0.9% saline. We studied a minimum of five sections per lung (total ten sections per person) regardless of the presence or absence of morphologically demonstrable lesions. Paraffin-embedded tissue sections were assessed following haematoxylin and eosin staining. In order to document the presence and distribution of the wide spectrum of infectious agents to which this population is susceptible, we prepared a variety of special stains (Periodic acid-Schiff test, immunohistochemistry analysis, fluorescence, Ziehl-Neelsen, Gram, Mucicarmine, and Gomori'smethenamine silver stain) for selected tissue sections. Bacterial bronchopneumonia (BBP) was defined as the presence of cell consolidation with polymerphonuclear leukocyte accumulation in bronchioles and adjacent alveoli. For the diagnosis of cytomegalovirus (CMV) and fungal pneumonia, histological evidence of lung involvement was required with or without tissue culture. Severe sepsis and/or septic shock were defined as sepsis with the addition of organ dysfunction or clinical diagnosis of arterial hypotension, which may or may not be responsible for the aggressive fluid resuscitation. Diagnosis of *Mycobacterium tuberculosis* infection and atypical mycobacterial infection was confirmed using fluorescence and Ziehl-Neelsen techniques, and Lowenstein-Jensen culture. The proportion method and biochemistry were used for identification of all positive cultures.

2.2. Statistical Analysis

Descriptive analyses of the data collected from 1990 to 2008 included median, minimum, and maximum values. The probability (odds ratio) that the major AIDS-associated diseases would develop a specific histopathological pattern was determined by logistic regression. All the statistical procedures were performed using SPSS v10.0 statistical software. Statistical significance was set at 5% (p value).

We calculated prevalences related to demographic and etiologic data from two different periods, too:

1) First period (from 1990 to 2000)—period before antiretroviral therapy advent and transition of initial application to population (n = 319 patients).

2) Second period (from 2001 to 2008)—period after effective antiretroviral therapy advent, when the ART was well established (n = 170 patients).

3. Results

3.1. Total Period of Study (1990 to 2008)

Demographic data from 1990 to 2008 are listed in **Table 1**. A total of 355 (72.6%) men and 134 (27.4%) women

Table 1. Demographic analysis by gender and age taken from autopsies of patients with HIV/AIDS whose cause of death was IRA between the years 1990 and 2008.

Age	Sex		Total
	Male	Female	
1 a 20	15	7	22
21 a 49	299	110	409
50 a 70	38	17	55
>70	3	0	3
Total	355	134	489

were included in the study. The age at the time of death was 21 to 50 years (409 patients) for most cases. Median age was 37.

We observed a single HIV/AIDS-associated disease in 174 (35.6%) cases, two diseases in 158 (32.3%) cases, three diseases in 81 (16.6%) cases, and four diseases in 29 (5.9%) cases. No HIV/AIDS-associated diseases were detected in 47 patients (9.6%).

The HIV/AIDS-associated diseases in patients with ARF are shown in **Table 2**. Between 1990 and 2008, BBP was present in 43.3% of patients (212 cases) and was the most frequent pulmonary complication found at the time of autopsy.

In the same period, the pulmonary histopathological analysis showed DAD in 31.1% of patients (152 patients), The pulmonary histopathological findings observed in different HIV/AIDS-associated diseases are shown in **Table 2**.

Table 2. Etiological diagnosis and histopathological pulmonary findings observed in lung autopsies of HIV-infected patients who presented IRA as cause of death, between 1990 and 2008.

Associated Diseases	DAD	PE	AH	AIP	Total
Bacterial bronchopneumonia	58	23	24	33	212
Pneumocistisjiroveci pneumonia	56	3	14	82	186
Sepsis and/or septic shock	105	6	22	30	194
Cytomegalovirosis	33	1	13	48	103
Disseminated tuberculosis	39	4	3	10	78
Toxoplasmosis	31	8	13	10	94
Pulmonary tuberculosis	36	5	10	9	87
Atypical mycobacterium tuberculosis	22	6	2	6	45
Kaposi sarcoma	19	2	6	11	52
Pulmonarythromboembolism	22	10	0	9	58
Neurocriptococcosis	6	2	0	8	17
Non-Hodkinlimphoma	5	6	3	3	17
Bacterialmeningitis	3	0	9	0	19
Limphoma	7	0	0	5	12
Histoplasmosis	7	0	4	0	11
Livercirrhosis	16	9	1	5	38
Schistossomosis	8	0	0	0	8
Acuteperitonitis	4	0	0	3	7
Bacterialendocarditis	4	0	0	0	4
Pulmonarycriptococcosis	3	3	1	0	10
Neurocisticercosis	2	2	0	4	8
Chronicpneumopathy	0	3	0	0	3
Pielonefritis	0	0	2	4	6
Disseminated neoplasy	2	0	0	2	4
Neuropathy	2	0	0	0	2
Duodenal ulcer	4	0	0	4	8
Acute Renal Failure	12	0	0	3	15
Chronicpancreatitis	4	3	7	3	17
Deepvenousthrombosis	4	0	0	0	4
Aspergilosis	0	0	0	0	1

*DAD = diffuse alveolar damage; PE = pulmonary edema; AIP = acute interstitial pneumonia; HA = alveolar hemorrhage.

Multivariate analysis with association between HIV/AIDS-associated diseases and histologic patterns is available in **Table 3**.

3.2. Comparing before and after ART' Periods

Demographic data from these periods can be verified in **Table 4**. In the first period we observed a prevalence of 21% women and 79% men, whereas in the second period these numbers were, respectively, 32% and 68%.

BBP was the most prevalent HIV/AIDS-associated disease in both periods, as we can observe comparatively in **Table 5**.

We observed the inversion in prevalence of AIP and DAD, in the first period AIP was more prevalent, and in the second, DAD was, as exposed in **Table 6**.

4. Discussion

This is the biggest study in autopsies that includes demographic data, etiologic diagnose and respective pulmonary histopathological records from HIV/AIDS patients, whose cause of death was ARF. Between 1990 and 2008, diagnose of HIV/AIDS was made in 489 autopsies. As comented, BBP was present in 43.3% and *Pneumocystis jiroveci* pneumonia in 38.0% of patients. The pulmonary histopathological patterns were, in descending order: DAD in 31.1% of patients, AIP in 23.5%, PE in 9.4%, e AH in 9.0% of patients. The multivariate analysis showed significant and positive association between DAD and: disseminated tuberculosis, liver cirrhosis e sepsis and/or septic shock; and between AIP and: Pneumocystis jiroveci pneumonia and cytomegalovirosis.

From the first descriptions of HIV/AIDS, the lung has been the site most often affected by the disease and its complications. Pulmonary involvement has been reported in 80% - 94% of patients with HIV/AIDS-associated diseases [10]. Despite recent technological advances in diagnosis, the autopsy has remained an important complementary tool for the identification and understanding of diseases in patients with HIV/AIDS [11]. Recent autopsy studies have shown important differences between autopsy findings and the clinical diagnosis *antemortem* in this group of patients [10-12].

In the present study, we observed a high prevalence (17.7%) of patients with HIV/AIDS who also had ARF as the cause of death. Most analyzed patients were males (72.6%) and the mean age was 37 years, similar with data from studies in other countries [10-14].

An autopsy study of patients with HIV/AIDS, performed in the United States, Afessa *et al.* showed the presence of two or more associated diagnoses in 52% of the cases studied, [11] what is consistent to the result of

Table 3. Multivariate analysis with major diseases found in autopsies of patients with HIV/AIDS, and their relationships with their respective lung histopathology.

	Pulmonary Histopathological Patterns											
	DAD			PE			AH			AIP		
Associated Diseases	p**	OR	CI 95%	p**	OR	CI 95%	p**	OR	CI 95%	p**	OR	CI 95%
Bacterial bronchopneumonia	NS	0.686	0.561 - 1.837	NS	1.293	0.708 - 2.361	NS	1.653	0.887 - 3.081	0.001	0.443	0.282 - 0.696
Pneumocistisjiroveci pneumonia	NS	0.753	0.451 - 1.255	0.005	0.177	0.042 - 0.745	NS	0.672	0.275 - 1.642	0.01	4.904	3.016 - 7.972
Sepsis and/or septic shock	0.015	2.987	1.83 - 4.875	NS	0.325	0.098 - 1.074	NS	1.157	0.517 - 2.593	NS	0.588	0.312 - 1.109
Cytomegalovirosis	NS	0.888	0.452 - 1.744	NS	0.198	0.027 - 1.468	NS	1.304	0.487 - 3.497	0.02	3.631	1.938 - 6.8
Disseminated tuberculosis	0.048	1.942	1.024 - 3.684	NS	0.708	0.21 - 2.368	NS	0.765	0.227 - 2.586	0.023	0.321	0.112 - 0.918
Toxoplasmosis	NS	1.028	0.517 - 2.044	NS	1.023	0.348 - 3.008	NS	1.464	0.543 - 3.945	NS	0.429	0.164 - 1.121
Pulmonary tuberculosis	NS	1.641	0.821 - 3.278	NS	0.536	0.125 - 2.305	NS	1.297	0.437 - 3.853	NS	0.387	0.134 - 1.12
Aypical micobacteriosis	NS	1.563	0.653 - 3.738	NS	2.202	0.713 - 6.801	NS	0.472	0.062 - 3.594	NS	0.315	0.073 - 1.369
Kaposi sarcoma	NS	1.277	0.524 - 3.111	NS	0.438	0.058 - 3.331	NS	1.648	0.468 - 5.806	NS	0.717	0.238 - 2.162
Pulmonary Thromboembolism	NS	1.188	0.493 - 2.865	NS	2.817	0.996 - 7.973	NS	0.949	0.928 - 0.969	NS	0.677	0.226 - 2.032
Limphoma	NS	3.36	0.56 - 20.317	NS	0.989	0.979 - 0.999	0.046	7.048	2.145 - 43.37	NS	2.201	0.363 - 13.33
Livercirrhosis	0.042	3.053	1.041 - 8.957	NS	1.6	0.347 - 7.375	NS	0.969	0.953 - 0.985	NS	0.537	0.118 - 2.435
Schstossomosis	NS	1.02	0.997 - 1.043	NS	0.993	0.986 - 1.001	NS	0.993	0.986 - 1.001	NS	1.64	0.147 - 18.26

*DAD = diffuse alveolar damage; PE = pulmonary edema; AIP = acute interstitial pneumonia; AH = alveolar hemorrhage; OR = odds ratio; CI = confidence interval; NS = not significant; **significant at $p < 0.05$.

Table 4. Demographic comparative analysis of age in before and after anti-retroviral advent found in autopsies of patients with HIV/AIDS whose cause of death was IRA.

Age	1990-2000		2001-2008	
	n	(%)	n	(%)
1a 20	18	5.64%	4	2.35%
21 a 49	277	86.83%	132	77.65%
50 a 70	22	6.90%	33	19.41%
>70	2	0.01%	1	0.01%

*n = number of cases.

55% we found. Hence, an important association between different pulmonary diseases in patients with HIV/AIDS and ARF was established, which could indicate the necessity of a different therapeutic strategy for these patients.

Comparing our results about the period of 2001 to 2008 with the period between 1990 and 2000, we observe some changes on HIV/AIDS' infection profile. First, there was a decrease of incidence of HIV-infected patients at autopsies, probably due to better efficacy and distribution of antiretroviral therapy, and recent technological advances in diagnosis. Although age between 21 and 40 years old remained the most affected by ARF as cause of death, there was a decrease in patients younger than 20 years old and an important increase in prevalence of patients older than 41 years old, confirming the aging of HIV/AIDS infected patients after the introduction of ART. Besides this, it seems to happen the feminization process of HIV infection, with an increase of prevalence rates of infected women from 21%, in the first period, to 27.4% in the second one.

There was an important increase of incidence of BBP (from 36% in the fist period to 47% in the second), sepsis and/or septic shock (from 14% to 22%), liver cirrhosis (from 1.2% to 13.5%). We observed a substantial decrease in prevalence rates of *Pneumocystis jiroveci* pneumonia (from 27% to 10%), cytomegalovirosis (from 13.2% to 5.8%), neurocriptococcosis (from 2.8% to 0%) and atypical mycobacteriosis (from 6% to 3.5%). The other diseases kept constant their prevalences in both periods, with negligible fluctuations.

BBP was the most often pulmonary disease found at autopsies in both decades, and was present in 43.3% of patients (212 cases). Patients with HIV are at increased risk for BBP [13,15,16]. Studies have reported greater than 17 times the incidence of bacterial pneumonia in HIV-infected patients compared to the general population [17]. Effects of HIV infection that predispose patients to lung infections include depletion of alveolar CD4 T cells, impairment of humoral immunity, and functional alterations of granulocytes and alveolar macrophages [18,19]. BBP may also be responsible for more than half of all cases of respiratory failure requiring ICU admission in HIV-infected patients [6]. In our study, we observed an increase in prevalence of BBP in the second period, after ART. The impact of HAART on the development of bacterial pneumonia requiring ICU admission is not entirely clear. Some studies have shown no major changes in the proportion of HIV-infected patients admitted to the ICU for bacterial pneumonia [20]. Other studies, however, indicate the increase in the incidence and mortality by bacterial infections in the second period [21]. The mortality rates of HIV-infected patients with BBP reached 20% in some estudos [13].

From 1990 to 2008, sepsis/septic shock was present in 40.0% of patients with HIV/AIDS. In the literature, the rates of hospitalization in intensive care units for sepsis and/or septic shock in patients infected with HIV range from 11% to 23% [8,22-24]. At the early decades of HIV, sepsis was responsible for over than 15% of seropositive cases admitted in intensive therapy [25]. After introduction of ART, there was a trend of increasing incidence and mortality due to sepse [3,20], representing 45% of hospitalizations [21]. These data are consonant with our study, which showed an increase in cases of sepsis in the post HAART. Patients with septic shock may have dysfunction of the adrenal glands. In HIV-infected patients, the direct activity of HIV in the adrenal glands, related opportunistic diseases that affect them, and the medications used to treat these patients may contribute to the failure adrenal [25,28]. Therefore, physiological parameters and personalized therapies for HIV-infected patients with sepsis/septic shock, need to be investigated [25-28].

After ART advent, a decrease in incidence of *Pneumocystis jiroveci* pneumonia has been a worldwide phenomenon. In literature, the incidence of *Pneumocystis jiroveci* pneumonia in HIV-infected patients is 7% to 24% [4,6,8,22,24,29,30]. Similar to literature, our study showed a decrease of prevalence rates from 27% to 10% in the period after ART. During the earliest days of the AIDS epidemic, PJP resulting in respiratory failure was an almost universally fatal illness [5]. While there have been considerable advances in the care of HIV-infected patients over the last years, PJP, although its decrease, remains one of the most common etiologies for respiratory failure requiring ICU admission in HIV-infected patients, and its mortality remains high [4,8,22,30-32].

Several recent studies have shown that between one quarter and one third of all ICU admissions of HIV infected patients are due to *Pneumocystis jiroveci pneumonia* [6,8,32].

Pulmonary tuberculosis was found in 17.8% of the cases in the whole period of our study. Autopsy studies have found the presence of *Mycobacterium tuberculosis*

Table 5. Comparing prevalences of diseases in the first (1990 to 2000) and second period (2001 to 2008).

Associated Diseases	1990-2000		2001-2008	
	n	(%)	n	(%)
Bacterial broncopneumonia	91	36.40%	81	47.60%
Pneumocistisjiroveci pneumonia	68	27.20%	17	10%
Sepsis and/or septic shock	34	13.60%	38	22.40%
Cytomegalovirosis	33	13.20%	10	5.80%
Disseminated tuberculosis	19	7.60%	14	8.20%
Toxoplasmosis	18	7.20%	14	8.20%
Pulmonary tuberculosis	17	6.80%	11	6.40%
Atypical micobacteriumtuberculosis	15	6.00%	6	3.50%
Kaposi sarcoma	11	4.40%	7	4.10%
Pulmonary thromboembolism	10	4.40%	9	5.30%
Neurocriptococcosis	7	2.80%	0	0.00%
Limphoma	4	1.60%	3	1.80%
Live cirrhosis	3	1.20%	23	13.50%
Acute renal failure	1	0.40%	5	2.90%
Pulmonary criptococcosis	2	0.80%	3	1.80%
Deepvenousthrombosis	1	0.40%	4	2.30%

*n = number of cases.

Table 6. Comparative prevalence of pulmonary histology found in the analyzed periods.

Histological patterns	1990-2000		2001-2008	
	n	(%)	n	(%)
AIP	127	39	24	19
DAD	114	36	68	53
AH	40	13	19	15
PE	37	12	17	13

*DAD = diffuse alveolar damage; PE = pulmonary edema, AIP = acute interstitial pneumonia, AH = alveolar hemorrhage; n = number of cases.

infection in 5% - 59% of cases [33-38]. Worldwide is known the importance of *mycobacterial tuberculosis* co-infection in HIV positive patients. In developed countries, the prevalence of tuberculosis in autopsies of patients with HIV/AIDS is much lower than developing countries, like Brazil [33-38].

CMV pneumonitis was found in 21.1% of patients. Comparing first and second period we observed a significant decrease of prevalence. Several autopsy studies in patients with HIV/AIDS have reported the presence of CMV infection in 7% - 81% of patient cases [10,12,18, 19,39-44]. CMV infection has been more frequently diagnosed at postmortem examinations than prior to death, what explains an important different between clinical prevalences and autopsy results [10].

Atypical mycobacterial infection had a prevalence of 9.2% of cases. It seems to be consistent to the literature, because our study included only patients dead due to ARF, and atypical mycobacterial pulmonary infection is not seen in increased frequency in these patients [19,37, 39,45]. There was a decrease in the prevalence of this infection after ART introduction.

About 7.0% of patients had cirrhosis. This is a high prevalence and it's certainly an underestimated number, because we included only ARF patients. As patients with HIV are living longer, they are at increasing risk of developing noninfectious complications and comorbid illnesses associated to HIV and to its treatment [46,47]. In the United States, in 2007, about 25% of the population infected with HIV were older than 50 years old, [48,49] and it's estimated that, by 2015, more than half of patients living with HIV will be older than 50 years [50]. Chronic diseases associated with aging such as cardiovascular, and liver diseases are more prevalent and may

progress more rapidly in HIV-infected patients [50-55]. Drug toxicities, coinfections with hepatitis B and hepatitis C viruses, and general medical conditions such as chronic pulmonary disease, renal insufficiency, cardiomyopathy, and cirrhosis account for a growing percentage of ICU admissions in HIV-infected patients, as we observed in our study [50-55].

Based upon pulmonary histopathological analysis, DAD was the most common pattern observed (31.1%), followed by AIP (23.5% of cases). In the first period, from 1990 to 2000, we noticed AIP was the most prevalent (40%), followed by DAD (36% of cases), when development of prevalent AIP was attributed to opportunistic infections (mainly viral, fungal and mycobacterial infections). The fact of DAD has became the first in prevalence in the second period (2001 to 2008) can be an effect of mechanical ventilation and of a decrease on the incidence of opportunistic infections due to specific treatment and a consequence of developing noninfectious complications and comorbid illnesses associated to aging (like cardiovascular, chronic pulmonary disease, renal insufficiency and liver diseases) that have been related with increased risk in HIV-infected older adults [46,47]. Besides this, sepsis, that was the second most important in prevalence showed high significant relation with DAD.

5. Conclusion

Consonant to literatures, our study revealed decrease of mortality by ARF related to some opportunistic infections associated with HIV/AIDS, probably due to effective combinations of ART. However, we observed an increase of the prevalence of BBP, sepsis and/or septic shock and liver cirrhosis, possibly secondary to known effects of mechanical ventilation and noninfectious comorbidities to that HIV/AIDS patients are more susceptible. Despite recent technological advances in diagnoses, the autopsy has remained an important complementary tool for the identification and understanding of diseases in patients with HIV/AIDS.

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