CLINICAL SCIENCE

Demographic, etiological, and histological pulmonary analysis of patients with acute respiratory failure: a study of 19 years of autopsies

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INTRODUCTION: Acute respiratory failure has been one of the most important causes of death in intensive care units, and certain aspects of its pulmonary pathology are currently unknown.

OBJECTIVES: The objective was to describe the demographic data, etiology, and pulmonary histopathological findings of different diseases in the autopsies of patients with acute respiratory failure.

METHOD: Autopsies of 4,710 patients with acute respiratory failure from 1990 to 2008 were reviewed, and the following data were obtained: age, sex, and major associated diseases. The pulmonary histopathology was categorized as diffuse alveolar damage, pulmonary edema, alveolar hemorrhage, and lymphoplasmacytic interstitial pneumonia. The odds ratio of the concordance between the major associated diseases and specific autopsy findings was calculated using logistic regression.

RESULTS: Bacterial bronchopneumonia was present in 33.9% of the cases and cancer in 28.1%. The pulmonary histopathology showed diffuse alveolar damage in 40.7% (1,917) of the cases. A multivariate analysis showed a significant and powerful association between diffuse alveolar damage and bronchopneumonia, HIV/AIDS, sepsis, and septic shock, between liver cirrhosis and pulmonary embolism, between pulmonary edema and acute myocardial infarction, between dilated cardiomyopathy and cancer, between alveolar hemorrhage and bronchopneumonia and pulmonary embolism, and between lymphoplasmacytic interstitial pneumonia and HIV/AIDS and liver cirrhosis.

CONCLUSIONS: Bronchopneumonia was the most common diagnosis in these cases. The most prevalent pulmonary histopathological pattern was diffuse alveolar damage, which was associated with different inflammatory conditions. Further studies are necessary to elucidate the complete pathophysiological mechanisms involved with each disease and the development of acute respiratory failure.

KEYWORDS: Acute Respiratory Failure; Autopsy; Lung Disease; Diffuse Alveolar Damage; Pulmonary Edema.

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INTRODUCTION

Acute respiratory failure (ARF) is a major cause of death in patients with a variety of primary underlying diseases. In addition, the prevalences of comorbidities and mortality have been reported to be higher than 40-50% in ARF patients, especially in those with diffuse infiltrates as seen on chest X-rays.[1-3] The clinical and radiological findings in ARF are nonspecific,[4-6] and prompt investigation and diagnosis are essential to improving patient survival.[7-9] In this context, the complexity of clinical presentations makes diagnosis a constant challenge for the clinician. Despite recent advances, most types of diagnostic support are still expensive. Clinicians often initiate treatment to avoid the rapid progression of the disease and to spare the patient from more invasive procedures. Therefore, it is important to determine the leading causes of death in this population to establish correct prophylactic actions, which is the least expensive strategy for preventing further pulmonary dysfunction and avoiding the need for lung biopsies.[10]

We performed a retrospective study of 4,710 autopsies on patients whose cause of death was ARF to better describe the demographic and etiological data and the associated histological pulmonary findings and diseases.

MATERIAL AND METHODS

Autopsies. This study was conducted at a tertiary health care center. From 1990 to 2008, 26,560 medical autopsies were performed at this center, with an annual mean of 1,889. We examined the autopsies of the 4,710 (17.7%) patients in whom ARF was the cause of death. In 980 of these patients, the histological pulmonary findings could not be reviewed because the pulmonary tissue was not available (it was classified as ''without analysis''); histological pulmonary analyses were performed in the remaining 3,730 (79.2%) cases. In this study, we reviewed all of the available microscopic and macroscopic diagnoses of death at autopsy, along with the patient medical records. The only inclusion criterion for the definition of ARF was based on arterial blood gases ($PaO2<60$ mmHg or $PaCO2>50$ mmHg with $pH<7.30$) while breathing room air.[1-3] We excluded patients younger than one year of age and individuals not diagnosed with ARF.

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

The clinical data from the patients enrolled in the study were collected with the approval of the Internal Review Board for this study, and informed consents were obtained from family members to perform the autopsies.

After a complete review, the pulmonary pathological reports were categorized as follows:

•diffuse alveolar damage (DAD), which was defined as diffuse involvement and a uniform temporal appearance of alveolar collapse, hyaline membranes, obliterative fibrosis, neo-septal formation, and moderately organizing fibrosis;

•pulmonary edema (PE), which was defined as the accumulation of proteinaceous fluid in the alveolar spaces that gave the appearance of a granular, pink coagulate within such spaces;

•alveolar hemorrhage (AH), which was defined as the presence of blood in the alveolar spaces; and

•lymphoplasmacytic interstitial pneumonia (LPIP), which was defined as widened and edematous alveolar septa, usually accompanied by a mononuclear inflammatory infiltrate of lymphocytes, histiocytes, plasma cells, and neutrophils.

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

Statistical analysis. The descriptive analysis of the data included median, minimum, and maximum values. The probabilities (odds ratios) that patients with underlying diseases and comorbidities would develop specific pulmonary histopathological patterns and die of ARF-related pulmonary alterations were determined by logistic regressions. The independent variables included the following major diseases and/or comorbidities: BBP, cancer, liver cirrhosis, HIV/AIDS, acute myocardial infarction, systemic arterial hypertension, dilated cardiomyopathy, pulmonary embolism, chronic obstructive pulmonary disease, diabetes mellitus, sepsis and septic shock, chronic kidney failure, and tuberculosis. All the statistical procedures were performed using the SPSS v10.0 statistical software. Statistical significance was set at a *p*-value of 5%.

RESULTS

ARF was described in 4,710 autopsies (17.7%) from 1990 to 2008. The patients' ages ranged from 1 to 99 years (with a median of 52). A total of 2,713 (57.6%) men and 1,997 (42.4%) women were included in the study. The demographic data are listed in Table 1.

We observed a single associated disease in 1,793 (38.0%) of the cases, 2 diseases in 1,505 (32.0%), 3 in 797 (16.9%), 4 in 349 (7.4%) and 5 diseases in 184 (3.9%) of the cases. A diagnosis could not be determined after autopsy in 82 (1.7%) of the cases.

The pulmonary histopathological analysis showed DAD in 40.7% (1,917) of the patients, PE in 23.5% (1,107), AH in 10.4% (491) and LPIP in 4.6% (215) of the patients. The pulmonary histopathological findings and the most prevalent diseases in the 4,710 patients are shown in Table 2.

The major underlying diseases and comorbidities in the ARF patients are shown in Table 2. BBP was present in 33.9% of the patients (1,597 cases) and was the most frequent pulmonary complication found at the time of autopsy. Cancer was the second most frequent complication; it was observed in 28.1% of the patients (1,324 cases), followed by severe sepsis and/or septic shock in 14.3% (675), liver cirrhosis in 13.6% (639), HIV/AIDS in 10.4% (490), pulmonary embolism in 9.0% (426), acute myocardial

Table 1 - The demographic analysis by sex and age of the patients with acute respiratory failure who underwent autopsies.

Age group (years)	Sex		Total
	Male	Female	
1 to 20	198	165	363 (7%)
21 to 49	1073	750	1823 (38.7%)
>50	1442	1082	2524 (53.5%)
Total	2713 (576%)	1997 (42.4%)	4710

Table 2 - The etiological diagnoses observed in the autopsies of the acute respiratory failure patients, along with the main pulmonary histopathological findings.

Disease	DAD	PE	AH	LPIP	Without analysis	Total	(%)
BBP	572	264	145	78	538	1597	33.9%
Cancer	500	280	157	36	351	1324	28.1%
Severe sepsis and/or septic shock	414	76	60	26	99	675	14.3%
Liver cirrhosis *	407	103	65	14	50	639	13.6%
Systemic arterial hypertension	172	181	52	13	123	541	11.5%
HIV/AIDS	152	47	44	115	132	490	10.4%
Pulmonary embolism	68	102	77	10	169	426	9.0%
Acute myocardial infarction	38	159	4	0	18	219	4.7%
Brain stroke	97	61	15	1	33	207	4.4%
Chronic kidney failure	88	56	21	7	35	207	4.4%
Diabetes mellitus	69	51	15	6	50	191	4.1%
Dilated cardiomyopathy	39	90	17	5	35	186	4.0%
COPD	35	39	20	3	67	164	3.5%
Tuberculosis	33	16	9	7	39	104	2.2%

* = No cause identified; DAD = Diffuse alveolar damage; PE = Pulmonary edema; AH = Alveolar hemorrhage; LPIP = Lymphoplasmacytic interstitial pneumonia; BBP = Bacterial bronchopneumonia; HIV/AIDS = Human immunodeficiency virus/acquired immunodeficiency syndrome; COPD = Chronic obstructive pulmonary disease.

infarction in 4.7% (219), stroke in 4.4% (207), and tuberculosis in 2.2% (104 cases) of the patients. The main associated comorbidities were systemic arterial hypertension in 11.5% (541 cases), chronic kidney failure in 4.4% (207), diabetes mellitus in 4.1% (191), dilated cardiomyopathy in 4.0% (186), and chronic obstructive pulmonary disease in 3.5% (164) of the patients.

The multivariate analysis, with the statistically significant associations between the most prevalent diseases/comorbidities and the different histopathological findings, is shown in Table 3.

DISCUSSION

The early and accurate treatment of ARF remains an important problem in the management of critically ill patients. Despite recent technological diagnostic advances, the autopsy remains an important complementary tool for identifying and understanding diseases. Autopsy studies have shown important differences between autopsy findings and the *antemortem* clinical diagnoses.[11-13] Such diagnostic disagreement can vary from 10% to 90%, depending on the disease and the population involved.[4-10,14-19] These discrepancies may be attributable to different clinical manifestations of a single disease or to poor-quality medical care.[4] Recently, ARF was reported to be one of the leading causes of morbidity and mortality in critically ill patients.[4,9,14-16] In this study, we observed a high prevalence (17.7%) of ARF patients. Most of the study patients were males (57%), and the mean age was 52 years. Others studies have shown similar results.[4,9,14-16] A retrospective study carried out between 1996 and 2002 in 58 patients with DAD diagnosed by surgical lung biopsy found that 52% of the patients were male and that the mean age was 61 years.[20]

We observed a single disease in 38% of the patients with ARF and two or more diseases in 62% of the patients. The

Table 3 - The multivariate analysis of the main associated diseases found in the autopsies of the patients with acute respiratory failure, showing the relationships with the respective pulmonary histopathological findings.

	DAD			PE			AH			LPIP		
	OR	*p***	CI 95%	*OR*	*p***	CI 95%	*OR*	*p***	CI 95%	*OR*	*p***	CI 95%
BBP	1.5	<0.001	1.31–1.72	1.64	<0.001	1.39–1.93	1.24	0.04	1.00–1.53	1.21	NS	0.88–1.65
HIV/AIDS	2.14	<0.001	1.72–2.68	2.04	<0.001	1.47–2.82	1.4	NS	0.99 – 1.97	10.05	<0.001	7.16–14.11
Severe sepsis and/or septic shock	2.67	<0.001	2.24–3.20	2.29	<0.001	1.77–2.96	1.19	NS	0.89 – 1.58	1.5	NS	0.95–2.37
Liver cirrhosis	2.24	<0.001	1.86–2.70	1.69	<0.001	1.33–2.14	1.06	NS	0.79 – 1.42	2.01	0.02	1.14–3.55
Cancer	1.09	NS	0.94–1.26	1.27	0.006	1.07–1.50	1.23	NS	0.99 – 1.52	1.33	NS	0.90–1.96
Pulmonary embolism	3.67	<0.001	2.79–4.85	1.22	NS	0.95–1.56	2.14	<0.001	1.62 – 2.82	1.64	NS	0.84–3.19
Acute myocardial infarction	3.14	<0.001	2.18–4.54	6.19	<0.001	4.50–8.52	5.67	0.001	2.08 – 15.44	4.94	NS	0.71–6.32
Systemic arterial hypertension	1.02	NS	0.73–1.44	1.3	NS	0.90–1.90	1.14	NS	0.67 – 1.94	0.54	NS	0.24–1.20
Dilated cardiomyopathy	2.3	<0.001	1.58–3.34	2.54	<0.001	1.84–3.49	1.05	NS	0.62 – 1.76	1.03	NS	0.41–2.60
COPD	2.04	0.001	1.36–3.05	1.38	NS	0.93–2.04	1.58	NS	0.96 – 2.60	1.4	NS	0.43–4.55
Diabetes mellitus	1.13	NS	0.81–1.58	1.07	NS	0.75–1.54	1.03	NS	0.64 – 1.64	0.95	NS	0.39–2.32
Chronic kidney failure	1.11	NS	0.82–1.51	1.38	NS	0.98–1.94	0.98	NS	0.61 – 1.57	1	NS	0.45–2.24
Tuberculosis	1.54	NS	0.98–2.40	1.22	NS	0.70–2.14	1.24	NS	0.61 – 2.49	1.48	NS	0.65–3.35

OR = Odds ratio; CI = Confidence interval; DAD = Diffuse alveolar damage; PE = Pulmonary edema; AH = Alveolar hemorrhage; LPIP = Lymphoplasmacytic interstitial pneumonia; BBP = Bacterial bronchopneumonia; HIV/AIDS = Human immunodeficiency virus/acquired immunodeficiency syndrome; COPD = Chronic obstructive pulmonary disease; NS = Not statistically significant; * = No cause identified.

high prevalence of multiple diagnoses illustrates the complexity and critical status of the patients that presented with ARF as the cause of death; it may indicate the need for a different therapeutic strategy with these patients.[21-22]

Our study specifically showed that the patients who developed ARF had underlying diseases such as BBP (33.9%), cancer (28.1%), sepsis and septic shock (14.3%), liver cirrhosis (13.6%), HIV/AIDS (10.4%), pulmonary embolism (9.0%), acute myocardial infarction (4.7%), brain stroke (4.4%), chronic kidney failure (4.4%), and diabetes mellitus (4.1%). Infectious diseases were the most common diagnoses, as has also been described by other authors.[6,9,14-20,23,24] Interestingly, these findings are not consistent with our previously published study in 2008 that reported related cases of ARF in autopsies from 1990 to 2000 only; it reported the following associated diseases or complications in descending order: HIV/AIDS (31.4%), BBP (21.8%), sepsis and septic shock (11.7%), liver cirrhosis (11.5%), pulmonary embolism (5.7%), acute myocardial infarction (5.5%), brain stroke (4.6%), tuberculosis (3.6%), cancer (2.3%), chronic kidney failure (1.9%), and leukemia (0.2%).[22]

BBP was present in 33.9% of the patients and was the most frequent pulmonary complication found during autopsy. Frequently, the ARF patients had BBP as the initial cause of pulmonary disease, but BBP often occurs as a complication of other pathologies, usually in immunocompromised and intubated patients. Other studies have described similar findings and reported BBP as the most common disease in ARF patients.[20,23-25] Gross et al[25] analyzed 234 autopsies of elderly patients and found that 33% of them had BBP, which is exactly the same prevalence observed in our study but in an elderly-only population.[25]

Cancer was the second most important complication diagnosis in our study; it was present in 28.1% of the autopsies. This incidence rate was higher than that observed in other studies.[25] The most interesting observation was the increase compared with the incidence found in our previously published survey (2.3%).[22] This finding suggests that the number of diagnoses and the severity of cancer presentations have increased. These patients had been exposed to immunocompromised conditions from the use of quimioterapic agents and anorexia. Both these conditions increase the risk of associated infections, which are one of the major causes of death in this population.[20,26] Consequently, pulmonary manifestations are one of the most common causes of death in these patients; there is a high incidence of BBP, including atypical bacterias.[20,25,26]

In this study, HIV/AIDS was present in 10.4% of the patients with ARF. Pulmonary involvement has been reported in between 80 and 94% of the patients with HIV/AIDS. The classical evolution of patients with HIV/AIDS to ARF and its importance have been reported in several other studies.[11-13,21,22] As in patients with cancer, immunocompromised conditions substantially increase the risk of infection. Associated bacterial BBP is the major cause of respiratory failure, but tuberculosis, cytomegalovirus and *Pneumocystis jiroveci* pneumonia are also important causes of pulmonary commitment.[11-13,21] In contrast to our previous publication, the rate of HIV/AIDS infection has declined over the last ten years from 16-31% to only 10.4%.[21,22] Modern diagnostic methods, antibiotics and antiretroviral therapy have been reported to be the major causes of this modification of the HIV/AIDS prevalence in critically ill patients.[21]

We observed liver cirrhosis in 13.6% of the autopsies in this study; a similar association in ARF patients was not found in the literature. We realize that liver cirrhosis can result in an immunocompromised or inflammatory status similar to that of other pathologies and predispose patients to infectious diseases.

Others diseases, such as pulmonary embolism and acute myocardial infarction, were significantly associated with ARF. The underdiagnosis of pulmonary embolism has been a significant problem in critical care units until recently.[22]

Based on the pulmonary histopathological analysis, DAD was the most common pattern observed (40.7% of cases), which is consistent with our previous study.[22] No similar results have been previously found in other studies of ARF patients. Parambil et al[20] described a 90% prevalence of DAD in patients with acute respiratory distress syndrome who underwent surgical lung biopsies.[20,27] However, these findings are consistent with the higher prevalence and the significant association with BBP of sepsis and/or septic shock, HIV/AIDS and other infectious and inflammatory diseases. Other contributing factors include impeded mechanical ventilation, which can accelerate the development of these histopathologies.[21,22] Unexpectedly, DAD was also associated with conditions such as liver cirrhosis, acute myocardial infarction, pulmonary embolism, dilated cardiomyopathy and chronic obstructive pulmonary disease. We did not find that this association has been reported elsewhere in the literature, and it probably indicates that a common inflammatory response is present in these distinct pathologies.

As expected, PE was mostly associated with myocardial infarction and dilated cardiomyopathy; regardless, isolated PE was still observed and was associated with almost all of the major diseases studied. PE was the most specific pattern in the cancer patients, a finding that has not been previously reported.

AH was present in 10.4% of the patients and was associated with BBP and pulmonary embolism. We think that the association with myocardial infarction is not as relevant because of the small number of patients (four cases). AH was also associated with severe pulmonary complications and the presence of large necrotic areas and hemorrhaging, as is expected to result in cases of massive pulmonary embolism.[22] One group has described pulmonary embolisms in 5% of the patients who died from ARF.[14] Two other groups have reported pulmonary embolisms in 14% and 20% of the patients who died from ARF.[15,16]

Finally, LPIP showed an important association and was the most specific pattern in the HIV/AIDS patients, a finding that has been previously reported.[11-13,21] These findings are consistent with the higher prevalence of opportunistic infections, mainly viral, fungal and mycobacterial, that frequently cause LPIP to develop.[21,28] Liver cirrhosis was also associated with LPIP, although the possible reasons are unknown.

Limitations

First and foremost, this was a retrospective study of medical records in which the quality of the information was inherently limited. The second limitation of our study is related to the interobserver variability, which is an issue even though all of the autopsies at our institution are performed by a resident pathologist and supervised by a senior pathologist, who also checks the histological analysis

to prepare the final reports. Different observers can have different opinions; some studies have shown significant interobserver variability in about 15% to 35% of the autopsies analyzed.[4,7] In addition, the accuracy of autopsy findings depends on the interest and skill of the pathologist.

CONCLUSIONS

Despite recent advances in diagnostic technological, the autopsy has remained an important complementary tool for identifying and understanding diseases in ARF patients. BBP was the most common diagnosis in our ARF patients, followed by cancer. The most prevalent pulmonary histopathological pattern was DAD, which was associated with different inflammatory conditions.

Further studies are necessary to elucidate the complete pulmonary pathophysiological mechanisms involved in each disease and in the development of ARF.

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