Clinical Investigation

Pulmonary Disease at Autopsy in Patients With the Acquired Immunodeficiency Syndrome

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To characterize the postmortem pulmonary disease and analyze the effectiveness of antemortem diagnosis, we examined the clinical records and autopsy material from 54 patients who died of the acquired immunodeficiency syndrome. At autopsy, all patients had pulmonary disease. One or more specific diagnoses were made in 53, including opportunistic infection, nonopportunistic infection, and Kaposi's sarcoma. Multiple postmortem pulmonary diagnoses were established in 37. Respiratory failure was the most common cause of death.

Of the 97 pulmonary disorders discovered at autopsy, only 31 were diagnosed before death. The frequency with which infections were diagnosed during life varied according to the organism, and was significantly higher for Pneumocystis carinii *than for cytomegalovirus or bacterial agents. Pulmonary Kaposi's sarcoma was diagnosed in only 7% of patients with autopsy documentation. The yield of diagnostic procedures also varied according to the disease present. Sputum culture was relatively effective in detecting* Cryptococcus neoformans *and* Mycobacterium avium-intracellulare, *fiber-optic bronchoscopy was extremely useful for diagnosing* P carinii, *and one or more diagnoses were provided in 4 of 7 patients who underwent thoracotomy, but significant disease including cytomegalovirus infection and pulmonary Kaposi's sarcoma was frequently missed. Although the spectrum of lung disease found at autopsy is similar to that observed during life, the frequency of some pathologic processes including cytomegalovirus infection and Kaposi's sarcoma may be underrepresented in antemortem series.*

(Wallace JM, Hannah JB: Pulmonary disease at autopsy in patients with the acquired immunodeficiency syndrome. West J Med 1988 Aug; 149:167-171)

The acquired immunodeficiency syndrome (AIDS) is frequently complicated by pulmonary disease.[1] Since the initial experience with AIDS, various severe pulmonary disorders other than pneumonitis due to *Pneumocystis carinii* have been noted. Thus, the differential diagnosis in patients with AIDS and pulmonary disease has been extended to include not only AIDS-related opportunistic infections but also Kaposi's sarcoma involving the lung, a variety of nonopportunistic infections, and lymphoproliferative processes such as lymphoid interstitial pneumonitis and lymphoma.[1-5] The situation has been further complicated by the observation that several pathologic processes may occur in the lung simultaneously.

Although most cases of *Pneumocystis* pneumonia have been readily diagnosed during life, documenting other pulmonary disorders has been more difficult.[1-3,6-8] Thus, information regarding the frequency and types of pulmonary pathologic processes that affect patients with AIDS may be complete only at autopsy. To examine the spectrum, frequency, and ability to diagnose pulmonary disease in patients dying with AIDS, we reviewed the reports and slides of 54 autopsies done at UCLA Medical Center. For each case, the postmortem data were correlated with diagnostic information available in the antemortem clinical record.

Methods

We reviewed the autopsy records of all patients reported in the UCLA Medical Center Autopsy Registry to have died with AIDS. Of the 56 patients thus identified, 54 fulfilled the criteria for the diagnosis of AIDS established by the Centers for Disease Control[9] and were included in the study. For each patient, details of the gross description and the pathologist's formulation of the cause of death were recorded.

The available microscopic material from each case was reviewed. Histologic sections of lung, lymph nodes, spleen, adrenal glands, and other tissue indicated in the autopsy record to be of interest were examined. The specific diagnoses and pathologic findings noted in each type of tissue were recorded. The number of hematoxylin and eosin-stained slides reviewed varied from 2 to 13 (mean 4.5) for lung tissue and from 3 to 12 (mean 5) for extrapulmonary tissue. In 45 cases, 1 or more Ziehl-Neelsen-stained slides from the lung and extrapulmonary sites were studied. In 48 cases, at least one lung section stained with Gomori's methenamine-silver nitrate solution was examined. Lung sections stained with Gram's stain in 22 cases and with periodic acid-Schiff stain in 19 cases were evaluated. Additional slides from the available tissue blocks were prepared when necessary.

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Presented in part at the annual meeting of the American Thoracic Society, May 1985, Anaheim, California.
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ABBREVIATIONS USED IN TEXT
AIDS = acquired immunodeficiency syndrome
CMV = cytomegalovirus

The results of cultures taken during the autopsies were compiled from records available in the UCLA Clinical Microbiology Laboratory. All but ten of the autopsies were done within 24 hours of death. Tissue for postmortem cultures was not taken in seven cases for which the time of autopsy was delayed. Lung tissue was cultured for mycobacteria in 47 cases (on Lowenstein-Jensen and Wallenstein plates and in Middlebrook 7H12 agar), aerobic bacteria in 40 cases (on blood, chocolate, and MacConkey's agar), fungi in 28 cases (in Sabouraud's agar and on inhibitory mold and liver infusion agar), and viruses in 45 cases (in human embryonic lung fibroblast, human foreskin fibroblast, and primary African green monkey cell lines).

To obtain a data base that would allow correlation of details of the antemortem diagnostic evaluation with the autopsy findings, the clinical record of each patient was reviewed. Of the 54 patients included in the study, 36 had been treated at UCLA Medical Center and 18 at a Southern California Kaiser Permanente facility.* Autopsy data were correlated with antemortem data to determine the frequency with which the pulmonary diagnoses made at autopsy was established during life and the diagnostic yield of pulmonary procedures carried out during the four weeks before death. The pulmonary diagnostic procedures included sputum collection, diagnostic thoracentesis, fiber-optic bronchoscopy, and diagnostic thoracotomy. During fiber-optic bronchoscopy, specimens of bronchial washings, brushings, and fluoroscopically guided transbronchial biopsies were obtained. Bronchoalveolar lavage was done during 12 fiber-optic bronchoscopies. Pulmonary specimens obtained antemortem were processed in the same manner as the autopsy specimens except, in addition, sputum and bronchoscopy smear or sediment preparations were fixed in a 95% ethanol solution and stained by the Papanicolaou technique; and sputum, bronchoscopy, and thoracotomy specimens were submitted for *Legionella* direct antibody fluorescent staining and cultured by the method of Edelstein.[10]

Results

Patient Population Studied

The study group consisted of 53 men and 1 woman. All 54 patients had at least 1 identifiable risk factor for the development of AIDS: 51 had a history of a homosexual life-style, 6 were illicit intravenous drug users, 3 had received blood transfusions within five years before the time that AIDS was diagnosed, 1 was a recent immigrant from Haiti, and 1 had a history of heterosexual contact with an intravenous drug abuser. The diagnosis of AIDS was based on the documentation of opportunistic infection in 25 patients, Kaposi's sarcoma in 2, and both opportunistic infection and Kaposi's sarcoma in 27. The age at the time of death ranged from 23 to 72 years (mean 38 years). The mean interval from the time AIDS was diagnosed to the time of death was 7.2 months (range less than 1 to 29 months).

Autopsy Findings

The cause of death determined at autopsy for each of the patients studied is shown in Table 1. Respiratory failure was the most frequent cause of death. Severe widespread pulmonary parenchymal disease associated with pulmonary infection, Kaposi's sarcoma, or both, occurred in all 41 patients in whom respiratory failure was considered a major cause of death. The cause of death was considered to be overwhelming sepsis or widespread Kaposi's sarcoma in nine patients and central nervous system disease in three. Substantial pulmonary disease was also noted in all but one of these cases. In one patient, the cause of death could not be determined from the findings at autopsy. The only pulmonary disease found in this patient was a small focus of Kaposi's sarcoma.

The intrathoracic pathologic processes found at autopsy are summarized in Table 2. All 54 patients had some form of pulmonary parenchymal disease. Diffuse alveolar damage[11] was observed in 35 patients (65%). The exudative phase of diffuse alveolar damage, characterized by interstitial edema and hyaline membranes, was noted in three patients. The proliferative phase, with regeneration of alveolar epithelium, interstitial inflammation, and fibrosis, was present in 18. In 14 patients, both exudative and proliferative phases were

TABLE 1.—*Cause of Death Determined at Autopsy in 54 Patients With the Acquired Immunodeficiency Syndrome*

Cause of Death	Number of Patients
Respiratory failure	31
Respiratory failure and sepsis	10
Sepsis	7
Central nervous system process	3
Overwhelming Kaposi's sarcoma	1
Overwhelming Kaposi's sarcoma and sepsis	1
Unable to determine	1

TABLE 2.—*Intrathoracic Disease Found at Autopsy in 54 Patients With the Acquired Immunodeficiency Syndrome*

Pathologic Process	Patients No.	Patients %
Pulmonary parenchymal	*54*	*100*
Diffuse alveolar damage	35	65
Bronchopneumonia	18	33
Kaposi's sarcoma	14	26
Focal interstitial inflammation	13	24
Hemorrhage	12	22
Pulmonary edema	6	11
Airway	*31*	*57*
Tracheobronchitis	25	46
Kaposi's sarcoma	4	7
Bronchiolitis obliterans	2	4
Bronchiectasis	2	4
Pulmonary vascular	*12*	*22*
Thromboembolic disease	11	20
Medial thickening or intimal proliferation	1	2
Lymphadenopathy	*28*	*52*
Kaposi's sarcoma	16	30
Infectious agent	5	9
Lymphoma	1	2
Pleural	*43*	*80*
Effusions	35	65
Adhesions	8	15
Kaposi's sarcoma (direct involvement)	3	6
Empyema	3	6

*I. Jeffry Strumpf, MD, assisted in obtaining clinical information on the patients treated in the Southern California Kaiser Permanente system.

represented in different areas of the lung sections. All 35 patients with diffuse alveolar damage had autopsy evidence of at least one pulmonary infection: cytomegalovirus (CMV) in 22 (63%), *P carinii* in 20 (57%), *Cryptococcus neoformans* in 5 (14%), *Mycobacterium avium-intracellulare* in 5 (14%), pyogenic bacteria in 2 (6%), and adenovirus in 1 (3%). Mechanical ventilation was used during the month before death in 18 (51%).

Among the 18 patients with early to extensive bronchopneumonia noted at autopsy, 6 had corresponding radiographic abnormalities before death. In 14 (26%) patients, pulmonary lesions of Kaposi's sarcoma similar to those of previous descriptions were noted.[3-5,8] Focal interstitial pneumonitis (focal mononuclear cell inflammation with or without interstitial fibrosis and no reactive pneumocytes) was found in 13 patients (24%). Of 12 (22%) patients with gross evidence of pulmonary hemorrhage, 4 had pulmonary Kaposi's sarcoma and 5 had thrombocytopenia—platelet count less than 100,000 per μl—documented during the month before death.

Tracheobronchitis, the most common airway abnormality, was nonspecific in all but one patient with ulcerative lesions due to CMV infection and one with the typical plaques of *Candida albicans* infection. Tracheobronchial involvement with Kaposi's sarcoma was observed in four patients and caused significant large airway obstruction in two. In two cases, bronchiolitis obliterans was associated with diffuse alveolar damage. In one of two patients with severe bronchiectasis, there was evidence of airway colonization without invasion by *Aspergillus fumigatus.*

Pulmonary vascular disease was not prevalent in this series, evidence of recent thromboembolic disease involving only small distal vessels in all but two patients being the most common finding.

Englargement of the mediastinal or hilar lymph nodes (or both), noted in half the patients studied, was most frequently due to invasion with Kaposi's sarcoma. In six patients, a specific cause for the lymphadenopathy was not found.

Pleural effusions were found in 35 patients (65%) and were bilateral in each case. The effusions were substantial—greater than 500 ml—in 16 patients. Of these, 13 had Kaposi's sarcoma involving the mediastinum or pleural surface (or both), 1 had mediastinal lymph node involvement with *C neoformans,* 1 had contiguous gram-negative bacillary pneumonia, and 1 had no specific cause found. The appearance of the pleural fluid—serous versus serosangineous—did not correlate with the cause of the effusion. Empyema, present in three patients, was associated with a chest tube in two and bacterial pneumonia in one.

Correlation of Autopsy and Antemortem Findings

Table 3 shows the pulmonary diagnoses made antemortem and postmortem and the frequency with which each of the postmortem diagnoses was missed during life. At least one specific pulmonary diagnosis was made at autopsy in all but one patient. Only 31 (32%) of the 97 postmortem diagnoses were made before death. In 53 patients who had one or more specific pulmonary autopsy diagnoses, all diagnoses were made antemortem in 16 (30%) and none were made antemortem in 21 (40%). In 16 patients (30%), at least one autopsy diagnosis was established correctly before death, but one or more coexisting process were not discovered until the autopsy was done.

The pulmonary disorders detected most frequently antemortem were *P carinii* and *C neoformans* pneumonia. None of the patients with *Pneumocystis* or cryptococcal pneumonia in whom the diagnosis had been missed antemortem had undergone a pulmonary diagnostic procedure in the month before death. Most of the cases of pneumonitis due to a specific bacterial agent or CMV and pulmonary Kaposi's sarcoma were missed during life. Yet, each was a common postmortem diagnosis. At autopsy, CMV pneumonitis, documented in 31 patients (57%), was encountered more frequently than *P carinii* infection. The frequency of intrathoracic Kaposi's sarcoma was greatly underrepresented during life. Of the 29 patients in this series with Kaposi's sarcoma, intrathoracic involvement was documented in 21 (72%). Within the thorax, the sarcoma involved lung parenchyma in 14 patients, mediastinal or hilar lymph nodes (or both) in 16, and the pleural surface in 3. In one patient, the mediastinum was the only demonstrable site of Kaposi's sarcoma. The eight patients with no intrathoracic involvement had relatively limited disease confined to the skin in seven, and to the skin and gastrointestinal tract in one.

The diagnostic yield of all pulmonary procedures carried out within a month before death is shown in Table 4. Sputum cultures were useful for documenting pulmonary infection due to *C neoformans* and *M avium-intracellulare* and for identifying pathogenic bacteria. Of the 43 fiber-optic bronchoscopies done, 19 (44%) provided at least one pulmonary diagnosis. Fiber-optic bronchoscopy was most useful for documenting the presence of *P carinii* pneumonia. Only 3 of 20 (15%) fiber-optic bronchoscopies done in patients with CMV pneumonitis provided specimens with diagnostic cytopathic changes. In no case was Kaposi's sarcoma or the organism responsible for bacterial pneumonia found by bronchoscopy. Diagnostic thoracotomies performed during the month before death provided at least one specific diagnosis in four of seven patients (57%), but in each case at least one diagnosis was missed. Diagnostic thoracotomy documented the presence of Kaposi's sarcoma in only one of three cases (33%) and CMV pneumonitis in only one of seven (14%).

Discussion

Although patients with AIDS frequently undergo pulmonary diagnostic procedures,[1,2,6,7] the results may be incomplete because of the complex nature of the disease and the

TABLE 3.—*Pulmonary Diagnoses Made Antemortem and Postmortem in 54 Patients With the Acquired Immunodeficiency Syndrome*

Diagnosis	Patients, No.*		
	Antemortem Diagnosis	Postmortem Diagnosis	Diagnoses Missed Antemortem, %
Pneumocystis carinii	15	21	29
Cryptococcus neoformans	4	7	43
Mycobacterium avium-intracellulare	5	11	54
Bacterial pneumonia	2	12	83
Cytomegalovirus†	4	31	87
Kaposi's sarcoma	1	14	93
Herpes simplex virus	1	1	0
Adenovirus	0	1	100

*Some patients had more than one diagnosis.
†Includes only patients in whom cytomegalovirus inclusion bodies were found in pulmonary specimens.

limited size of the specimens. In this study, information available at autopsy was correlated with the results of antemortem diagnostic evaluations. The objectives were to better define the types and frequency of pulmonary disorders in patients with AIDS and to provide a clearer perspective of the currently available diagnostic capabilities. The findings indicate that many patients dying with AIDS have significant pulmonary disease that has been undiagnosed during life.

All of the patients in this series had some form of pulmonary disease, and all but one had at least one specific pulmonary diagnosis made during the postmortem examination. The most frequent cause of death was respiratory failure. These findings emphasize the high frequency and important role of pulmonary complications in the morbidity and mortality of AIDS. The spectrum of pulmonary disease found at autopsy in this series was the same as that reported previously in antemortem studies.[1,2] The striking finding in our study was that most patients had more than one coexisting pathologic process, most of which were unrecognized during life.

Missed antemortem diagnoses were most frequently those of CMV pneumonitis, bacterial pneumonia, or pulmonary Kaposi's sarcoma. More than half of our patients had cytopathic changes in pulmonary autopsy tissue consistent with CMV infection. The frequency with which CMV pneumonitis has been reported in AIDS patients has been considerably greater in autopsy series[3-5] than in antemortem studies,[1,6,7] reflecting the difficulty of diagnosis during life. In our series, only four patients had cytopathic evidence of CMV pneumonitis observed in pulmonary specimens taken during life, although it was found at autopsy in 31. By contrast, *Pneumocystis* pneumonitis was very effectively diagnosed by fiber-optic bronchoscopy during life. The only patients in whom *P carinii* was missed were those who did not undergo an appropriate evaluation. Other opportunistic pulmonary infections frequently detected during life included those due to *C neoformans* and *M avium-intracellulare.* Sputum collection or bronchoscopy appeared to be a relatively sensitive means of detecting these infections.

The occurrence of common pyogenic bacterial pneumonia in patients with AIDS is now well recognized.[12] Although bacterial pneumonia may have developed as an immediate preterminal event in some of our patients, consistent radiographic findings were documented before death in six. Identifying the responsible bacterial agent before death was difficult, the organism being correctly defined by the sputum culture in only two patients and by fiber-optic bronchoscopy or diagnostic thoracotomy in none.

Intrathoracic Kaposi's sarcoma, a common finding among patients with this malignant disorder, was also greatly underdiagnosed during life. The most frequent intrathoracic sites were the mediastinum and the lung parenchyma. Kaposi's sarcoma was the most common cause of mediastinal lymphadenopathy in this series. All but 3 of our 16 patients with notable pleural effusions had Kaposi's sarcoma, of whom only 2 had direct pleural involvement and 12 had extensive mediastinal involvement. Lymphatic obstruction from mediastinal tumor retards absorption of pleural fluid and is a well-recognized cause of pleural effusion.[13] According to the experience reported here, Kaposi's sarcoma involving the mediastinum is an important cause of pleural effusion in patients with AIDS.

Documenting pulmonary Kaposi's sarcoma during life may be difficult.[3,8] In our series, it was diagnosed antemortem in only 1 of 14 patients. Although the diagnosis has been established by transbronchial biopsy,[14] most reports emphasize the necessity of obtaining larger specimens by thoracotomy.[1,8] Even an open approach can fail to provide the diagnosis. In this study, pulmonary Kaposi's sarcoma was detected in only one of three patients who underwent diagnostic thoracotomy. The presence of skin lesions is an important diagnostic clue indicating that pulmonary disease may be due to Kaposi's sarcoma. All but one of our patients with intrathoracic involvement had skin manifestations.

In addition to the specific diagnoses discussed here, many of the patients in this series had nonspecific pathologic processes that contributed to the development of respiratory failure. Diffuse alveolar damage was noted in 35 patients. The histologic findings of this disorder represent a nonspecific reaction to a variety of insults that cause alveolar epithelial and endothelial cell injury.[11] Pulmonary infection was present in all of our patients who had diffuse alveolar damage. Mechanical ventilation with high concentrations of oxygen or sepsis or both are additional factors that may have contributed to the development of diffuse alveolar damage in some of our patients. Pulmonary hemorrhage, another nonspecific pulmonary complication observed by autopsy, occurred in 12 patients, 4 with pulmonary Kaposi's sarcoma and the rest with various infections. Previous reports[3-5,8] have documented the occurrence of pulmonary hemorrhage in patients with Kaposi's sarcoma. Five of our patients with thrombocytopenia were predisposed to intra-alveolar

TABLE 4.—*Diagnostic Yield of Pulmonary Procedures in 54 Patients With the Acquired Immunodeficiency Syndrome*

Diagnosis	Procedures, No. Diagnostic/No. Performed (%)*					
	Sputum Collection		Fiber-optic Bronchoscopy		Diagnostic Thoracotomy	
Pneumocystis carinii	ND		14/14	(100)	2/2	(100)
Cytomegalovirus†	0/14	(0)	3/20	(15)	1/7	(14)
Cryptococcus neoformans‡	3/4	(75)	1/1	(100)		ND
Mycobacterium avium-intracellulare‡	4/6	(67)	3/5	(60)	1/3	(33)
Bacterial‡	2/5	(40)	0/5	(0)	0/2	(0)
Kaposi's sarcoma	ND		0/8	(0)	1/3	(33)

ND=not done

*All procedures were carried out within 4 weeks before death.
†Only specimens showing cytomegalovirus inclusion bodies were considered diagnostic.
‡Specimens showing the organism microscopically, in culture, or both were considered diagnostic.

bleeding as a complication of pulmonary infection. The possibility of pulmonary hemorrhage should be considered in patients with AIDS who experience rapid respiratory deterioration. Although 11 of our patients (20%) had evidence of recent pulmonary emboli, only small distal vessels were involved in all but two. Thus, it is unlikely that thromboembolic disease contributed significantly to morbidity or mortality in most of our patients.

In conclusion, we emphasize that pulmonary disease in the patient with AIDS often is not completely characterized by one or even two diagnoses. Coexisting infection particularly due to CMV, Kaposi's sarcoma, or nonspecific pathologic processes such as diffuse alveolar damage or pulmonary hemorrhage may complicate what would superficially appear to be a clearly defined disorder. In some cases, the complete pulmonary diagnosis may require invasive procedures or an extended period of time for identifying a pathogenic organism. Therefore, a diagnostic strategy aimed at defining the pulmonary disease as thoroughly as possible must be planned early in the evaluation. As newer and possibly more effective treatment modalities for the various pulmonary complications of AIDS become available, refinement of the diagnostic process will become increasingly important.

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Book Review

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

Management of Spinal Cord Injuries

Edited by Ralph F. Bloch, MD, PhD, FRCP(C), Associate Professor of Medicine, McMaster University Faculty of Health Sciences, and Director of Neurotrauma Program, Chedoke Rehabilitation Centre, and Mel Basbaum, MSW, Social Work Department, Chedoke-McMaster Hospital, Chedoke Rehabilitation Centre, Hamilton, Ontario, Canada. Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202, 1986. 447 pages, $53.50.

The reluctance with which I embarked on fulfilling my commitment to writing a review of this book changed to delight as soon as I encountered the crisp clarity and insight in its pages.

"Injuries to the spinal cord are among the most devastating physical insults an individual may suffer. They spare the mind, leaving intact all desires and aspirations, while rendering the body unable to obey many, if not most, of the commands necessary to achieve these goals.

"Of course tragedy still holds center stage in many cases. But with ideal management combined with the buoyant will of most human beings, many patients with spinal cord injuries bounce back with a vigor that never fails to thrill me."

A frank appraisal of controversies in neurosurgical and orthopedic management sets the pace for a critical review of the literature, combined with the opinions and experience of a multidisciplinary team of authors from Canada, England, and the US. The chapters on pain, autonomic dysfunction, respiratory pathophysiology, gastrointestinal complications, urinary tract infections, sexual function, and resocialization deserve particular praise for their concise, candid styles and thoroughness. Each chapter resembles an epitome of progress in spinal cord injury management.

The book is an excellent resource for physicians and allied health professionals who treat paraplegics and quadriplegics on a regular or even an occasional basis. It highlights the medical, technologic, and attitudinal advances through which tragedy often gives way to brilliant successes. In the words of Dr Frank Krusen, one of the fathers of rehabilitation medicine, "Now that we have added years to life, let us add life to years."

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