JACC Vol. 11, No. 4
April 1988:792–9

MORPHOLOGIC STUDIES

Prevalent Myocarditis at Necropsy in the Acquired Immunodeficiency Syndrome

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The prevalence of myocarditis was retrospectively evaluated in 71 consecutive necropsy patients who died from acquired immunodeficiency syndrome (AIDS) between 1982 and 1986. Myocarditis was found in 37 cases (52%). Biventricular dilation at necropsy was present in seven cases (10%) and was accompanied by myocarditis in each case; fatal congestive heart failure occurred in four of these seven cases. Although viral, protozoan, bacterial, fungal and mycobacterial opportunistic pathogens were present in myocardial sections of 7 of 37 myocarditis cases, the etiology of myocarditis in the majority of these patients with AIDS remained idiopathic. Thus, myocarditis is a frequent finding at necropsy in patients with AIDS and may contribute to the development of biventricular dilation.

(J Am Coll Cardiol 1988;11:792–9)

Cardiac complications of the acquired immunodeficiency syndrome (AIDS) include pericardial effusion with or without tamponade, fibrinous pericarditis, fungal and viral myocarditis, marantic endocarditis, ventricular dilation or hypokinesia and Kaposi's sarcoma (1–7). These abnormalities are not clinically prominent and generally have not posed significant management problems. Recently, we described (8) three patients with AIDS in whom clinical, echocardiographic and morphologic findings of dilated cardiomyopathy were associated with cardiac insufficiency and death. In the two necropsy cases, focal myocarditis with diffuse myofibrillar loss and myocyte atrophy were found in the absence of identifiable infectious pathogens or Kaposi's sarcoma. Because the prevalence, clinical significance and etiology of myocarditis among patients with AIDS remains unknown, we retrospectively studied 71 patients who died from AIDS to determine the frequency of myocarditis and biventricular dilation at necropsy. The pathogenesis of these lesions and their contribution to mortality were investigated. The results of these studies indicate that myocarditis is a frequent and largely unexplained finding at necropsy and accompanies an increased prevalence of fatal cardiac dysfunction in the terminal course of patients with AIDS.

Methods

Selection of patients. Clinical and necropsy protocols of consecutive patients dying from AIDS between October 1981 and July 1986 at the Clinical Center of the National Institutes of Health (NIH), Walter Reed Army Medical Center, Washington, D.C. area hospitals were reviewed. Seventy-one patients satisfied the following criteria: 1) they met revised Center for Disease Control criteria for AIDS (9), 2) a detailed description of clinical history and hospital course was available for review, 3) necropsy was performed with no limitations on examination of the thorax or abdomen, 4) a detailed gross and microscopic description of the heart and lung was available for review, and 5) sections of heart were available for review and special stains were performed on all sections.

Of 90 patients screened, 71 met these criteria for study

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Manuscript received March 24, 1987; revised manuscript received November 11, 1987, accepted November 18, 1987.

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0735-1097/88/$3.50

and included 58 patients from the NIH Clinical Center with the following treatment protocols: 1) interferon, 21 patients; 2) interleukin-2, 7 patients; 3) chemotherapy (including doxorubicin) for cutaneous or visceral Kaposi's sarcoma, or both, 17 patients; 4) experimental antiviral agents heteropolyanion tungsten (HPA) or suramin sodium, 3 patients; 5) trimetrexate therapy for *Pneumocystis carinii* pneumonia, 5 patients; and 6) 5 patients chosen for study of immune ab normalities. The 13 patients from Walter Reed and other Washington area hospitals were not enrolled in clinical protocols.

Clinical definitions. *Cause of death* was evaluated from a comparison of the terminal clinical history with necropsy findings and was classified as:

1. *Respiratory death:* clinical respiratory failure in the setting of severe pneumonitis or widely disseminated pulmonary Kaposi's sarcoma each diffusely involving the lungs.
2. *Cardiac death:* death resulting from congestive heart failure, ventricular tachycardia or sudden death.
3. *Septic death:* death occurring as a result of refractory systemic hypotension (mean arterial blood pressure <60 mm Hg) and concurrent culture-proved sepsis.

Congestive heart failure was diagnosed if there was a compatible clinical history (dyspnea with pulmonary rales, systemic venous hypertension or an S_3 gallop) and one of the following: a decreased ejection fraction (≤45%) on either scintigraphy or two-dimensional echocardiography or decreased percent fractional shortening (<20%) on M-mode echocardiography.

Control cases. Hearts from 24 victims of sudden traumatic death served as control hearts. These were taken from the files of the Armed Forces Institute of Pathology and were selected according to the following criteria: 1) sudden traumatic death; 2) no known past medical history referable to the heart; 3) no history of intravenous drug abuse; 4) male/female ratio >10:1 and age range 18 to 59 years; 5) no gross traumatic damage to the heart and 6) no evidence of valvular or congenital abnormalities.

Examination of the heart. Gross examination of the heart was performed after fixation in 10% buffered formalin solution for ≥24 h in all 24 cases of sudden traumatic death and in 40 of the 71 AIDS cases. Heart weight, ventricular wall dimensions, presence of valvular abnormalities, extent of atherosclerotic involvement of coronary arteries and gross myocardial fibrosis or necrosis were assessed by visual inspection. Right ventricular dilation was considered present when the right ventricle represented more than two-thirds of the anterior surface of the heart or the right ventricle extended into and contributed to the formation of the apex, or both. The left ventricular transverse dimension was measured at the inferior border of the anterior mitral valve leaflet exclusive of the papillary muscles; the mean value ± SD for 24 cases of sudden traumatic death was 2.5 ± 0.6 cm. Left ventricular dilation was initially assessed by visual examination only; subsequently the transverse diameter was measured in the 40 cases available for repeat examination and dilation considered present when it was ≥4.0 cm. Data for lung weight in 35 patients and pericardial effusion in 69 patients were available from autopsy protocols.

Histology. In all traumatic death cases and in 28 AIDS cases, seven sections of myocardium were taken, including left ventricle (n = 2), ventricular septum (n = 1), right ventricle (n = 1), right and left atrium (n = 1 each) and mitral valve (n = 1). In 31 AIDS cases, a gross description of the heart was obtained from necropsy protocols. Sections of left ventricular myocardium (with or without right ventricle) were reviewed by pathologists who did not know the clinical history as follows: one section in 27 cases, 2 sections in 11 cases, three sections in 5 cases and seven sections in 28 cases for patients with AIDS and seven sections in all 24 cases for patients who died from traumatic death.

On two separate occasions, hematoxylin-eosin–stained myocardial sections were evaluated for each of four histopathologic processes as follows: 1) atrophy: a grade of 0, 1+, 2+ or 3+, respectively, was given if <5%, >5 but <25%, >25 but <50% and >50% of myocytes contained lipofucsin. Myofibrillar loss and a decrease in myocyte size were similarly graded for no change (0) or a mild [1], moderate [2] or severe [3] decrement. Atrophy was diagnosed when the average sum of the three numerical grades was ≥7. *2) intranuclear viral inclusions (Cowdry type A). 3) myocarditis defined by the Dallas criteria (10)* as myocyte degeneration or necrosis associated with adjacent inflammatory infiltrate. We required at least two foci per case and five or more inflammatory cells present per focus in a distribution described as focal, diffuse or confluent. *4) Fibrosis* was evaluated on Masson trichrome-stained sections. *5) Special stains for fungal and mycobacterial pathogens* were carried out on hearts of all patients who died with AIDS or sudden traumatic death.

Interobserver variability in diagnosing myocarditis was assessed between two cardiovascular pathologists (R.V. and M.R.) in 26 AIDS cases (one myocardial section per case). Each pathologist was unaware of the other's opinion at the time of diagnosis.

Data analysis. Associations among pathologic findings in patients with AIDS and between findings in AIDS and sudden traumatic death patients were tested by chi-square contingency tables or Fisher's exact test for discrete variables and Student's *t* test for continuous variables. Interobserver variability in the diagnosis of myocarditis was tested by computing the kappa statistic and its variance for the pair of observers (11). Values are expressed as mean ± SD.

Results

Patient characteristics (Table 1). Necropsy protocols or inpatient charts, or both, were reviewed in all cases. The clinical and demographic data document a predominantly

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Table 1. Clinical Characteristics of 71 Autopsy Patients With AIDS

					Total
Age range (years)	20 to 29	30 to 39	40 to 49	50 to 59	20 to 59
No. of patients	14	32	19	6	71
Men	13	29	19	6	67
Women	1	3	0	0	4
Risk factors					
Homo/bisexual	10	24	16	3	53
IV drug abuse	1	4	0	0	5
Other*	3	4	3	3	13
Opportunistic pathogens†					
Fungal	6	17	17	1	41
Mycobacterial	5	16	6	3	30
Protozoan	8	28	17	4	57
Viral	9	29	17	4	59
Tumors					
Kaposi's sarcoma	7	13	12	3	35
Lymphoma‡	0	1	0	0	1

*Other risk factors include: Haitian = 1, heterosexual promiscuity with prostitutes = 2, heterosexual contact with AIDS patient = 1 and all risk factors denied = 9. †Opportunistic pathogens are given in numbers of diagnoses. The most common pathogens for each type of infection are fungal: *Candida* spp. (35/441); mycobacterial: *M. avium intracellulare* (25/30); protozoan: *Pneumocystis carinii* (43/51); and viral: cytomegalovirus (52/59); ‡Lymphoma = non-Hodgkin's lymphoma, large cell, diffuse. IV = intravenous.

male homosexual study group who suffered from multiple opportunistic infections. The mean duration of disease from diagnosis of AIDS to death was 365 ± 196 days and did not significantly vary as a function of age. Patients who had a sudden traumatic death had a lower mean age (32 ± 8 years) and lower male/female ration (11:1) as compared with patients who died of AIDS (38 ± 8 years and 23:1, respectively).

Cause of death. The most common cause of death of the 71 patients with AIDS was pulmonary failure or pneumonia (45 patients) and cerebral necrosis with or without herniation (10 patients). Five patients died of cardiac causes (three died from congestive heart failure, one from ventricular tachycardia and one from sudden death). In addition, congestive heart failure was a contributory cause of death in one other patient. Seven patients died of sepsis, including three patients with biventricular dilation at necropsy. Four patients died of other causes, including pulmonary thromboembolism (n = 1), renal failure (n = 1) and undetermined except as AIDS (n = 2).

Gross cardiac findings (Table 2). Heart weight in AIDS patients was not significantly decreased compared with that in patients with sudden traumatic death. Significantly reduced heart weight (<250 g) was found in 12 patients and was associated with cachectic habitus ($p < 0.02$).

Right ventricular dilation in the absence of left ventricular dilation was found in 12 AIDS patients. This finding was associated with right ventricular hypertrophy (wall thickness ≥0.5 cm) ($p < 0.05$), pericardial effusion ≥75 ml ($p < 0.01$) and *P. carinii* or cytomegaloviral infection, or both, of lung ($p < 0.05$). Isolated right ventricular dilation was also associated with pulmonary failure as a cause of death in 11 ($p < 0.03$).

Biventricular dilation occurred in seven AIDS patients (Fig. 1), in five of whom the mean left ventricular transverse

Table 2. Necropsy Findings in 71 Patients With AIDS

					Total	Traumatic Death Patients
Age range (years)	20 to 29	30 to 39	40 to 49	50 to 59	20 to 59	18 to 48
No. of patients	14	32	19	6	71	24
Cachectic habitus	6	18	10	3	37	0
Heart weight (g)	294 ± 58	318 ± 72	360 ± 64	338 ± 103	326 ± 69	363 ± 89
RV dilation*	3	4	5	0	12	0
BV dilation†	3	3	1	0	7	0
P. effusion‡	5	8	2	0	15	0
Myocarditis	5	19	10	3	37	1
Myocardial opportunistic pathogens§	0	6	2	1	9	0
Atherosclerosis ‖						
0 to 25%: 3 CA	14	31	18	5	68	8
51 to 75%: 2 CA	0	1	1	1	3	11
76 to 100%: 2 CA	0	0	0	0	0	5

*RV dilation = right ventricular dilation alone; †BV dilation = biventricular dilation; ‡P. effusion = pericardial effusion >75 ml; §Myocardial opportunistic pathogens = histologically identifiable in myocardial sections: acid-fast bacilli = 2, Cowdry type A inclusion bodies = 2; gram-positive cocci = 1, fungal spores consistent with *H. capsulatum* = 1, *Candida* spp. = 1, protozoan organisms consistent with *T. gondii* = 2; ‖ extent of cross-sectional area luminal narrowing in three major coronary arteries (CA).

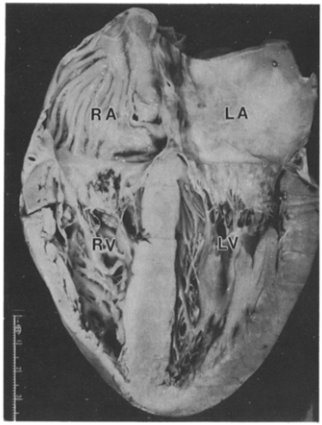


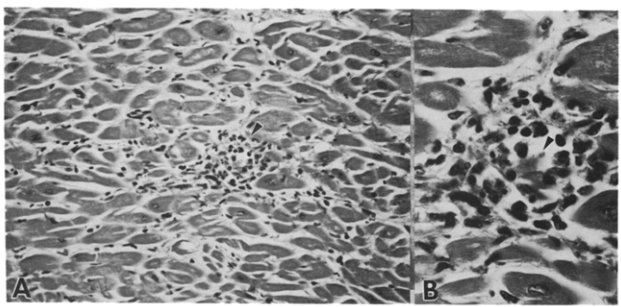
Figure 1. Heart of a 40 year old homosexual man who died as a result of septic shock secondary to *Pseudomonas* sepsis. The heart at autopsy weighed 400 g and there was four chamber dilation (four chamber view, left ventricular transverse diameter = 4.2 cm) in the absence of macroscopic necrosis or fibrosis. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

Figure 2. Photomicrographs showing a typical lesion of myocarditis in the left ventricle of a patient with AIDS. A, Note that the lesion is focal and small. B, Higher magnification of the lesion showing myocyte necrosis (arrow). (Hematoxylin-eosin; original magnification: A, ×250; B, ×600, reduced by 15%.)

dimension was 4.3 ± 0.4 cm (range 4.1 to 4.7). In two patients, one observer (W.C.R.) assessed biventricular dilation by visual inspection only. The mean transverse diameter for 35 AIDS patients without left ventricular dilation was 2.6 ± 0.5 cm (range 1.8 to 3.7). Left ventricular dilation occurred only in the setting of biventricular dilation. Biventricular dilation was positively associated with pericardial effusion ≥75 ml ($p < 0.01$) and increased heart weight (379 ± 42 g among AIDS patients versus 321 ± 73 g for AIDS patients without biventricular dilation, ($p < 0.05$). There was, however, no association between biventricular dilation and cardiomegaly (heart weight >400 g) as defined for the general population (12). Similarly, no significant association was found between biventricular dilation and disease duration, opportunistic pathogens, Kaposi's sarcoma or any one or combination of medications.

Myocarditis was present in all cases of biventricular dilation. However, myocarditis was not associated with isolated right ventricular dilation, pericardial effusion or epicardial Kaposi's sarcoma.

Histologic findings (Table 2). Focal mild myocarditis was found in 37 of the 71 AIDS patients (Fig. 2) and 1 of the 24 patients with sudden traumatic death. The association of myocarditis with AIDS was significant ($p < 0.01$). Its presence was not associated with a disease duration significantly different from that in AIDS patients without myocarditis. The number of foci of myocarditis varied from two to seven per section (mean 3 ± 2). The frequency of myocarditis was not dependent on the number of left ventricular sections taken per case, but was more often found in the left ventricle than in the right ventricle, ventricular septum or either atrial wall ($p < 0.05$). Myocarditis was not associated with any one or combination of opportunistic pathogens or drugs. The kappa statistic for the agreement between observers in the diagnosis of myocarditis was significant at the $p < 0.03$ level,



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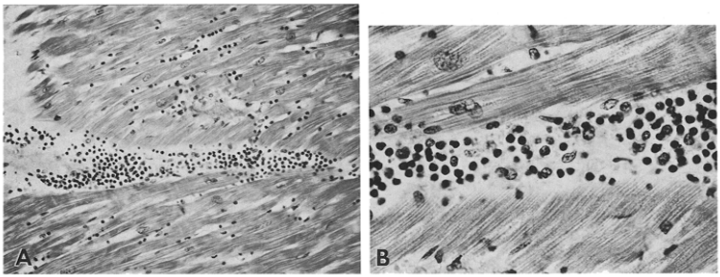

Figure 3. Photomicrographs of the left ventricle from a control sudden traumatic death victim. A, Note the interstitial inflammatory infiltrate consisting predominantly of lymphocytes. B, Higher magnification from the same area. Note the absence of myocardial necrosis. (Hematoxylin-eosin; original magnification: A, ×160; B, ×600, reduced by 26%.)

indicating that the extent of agreement was not a chance occurrence. There was total agreement in 22 of 26 cases in which 10 were diagnosed as myocarditis.

Focal mild interstitial mononuclear inflammatory cell infiltrates in the absence of myocyte injury were found in 10 (42%) of the 24 sudden traumatic death patients (Fig. 3) and 22 (31%) of the 71 AIDS patients. Because these foci were not associated with myocyte necrosis or degeneration, they were not diagnosed as myocarditis. In addition, myocardial sections from patients with AIDS that contained such infiltrates were no more likely to manifest myocarditis elsewhere in the tissue section than were sections without infiltrates. Furthermore, inflammatory cell infiltrates in the absence of myocyte injury were not found more frequently in AIDS patients as a group when compared with patients with sudden traumatic death. Interstitial fibrosis was generally lacking in myocardial sections from the heart of both patients with AIDS and those with sudden traumatic death.

Seven patients had histologic evidence of significant myocardial atrophy; five had been cachectic. Myocardial atrophy was associated with decreased heart weight ($p < 0.01$).

A variety of opportunistic pathogens were histologically identifiable in myocardial sections from nine AIDS patients, all of whom had systemic infection by the corresponding microorganism. In two patients (one with acid-fast bacilli in the myocardial interstitium and one with gram-positive cocci), the infectious organisms were surrounded by both acute and chronic myocarditis. Of the remaining seven patients, five had a focal mild myocarditis that was not found adjacent to the opportunistic pathogen (Fig. 4) and two had no evidence of myocarditis. Fibrinous pericarditis was found in three patients and epicardial Kaposi's sarcoma in seven.

Clinical correlates in patients with biventricular dilation at necropsy. Seven patients manifested biventricular dilation at necropsy; clinical congestive heart failure caused or contributed to death during the hospital course of four of these seven patients. The onset of congestive heart failure began within the final third of their AIDS-related illness (total illness duration 182 to 705 days) and lasted as long as 60 days. The association between biventricular dilation at necropsy and cardiac death was significant ($p < 0.03$).

Three patients with biventricular dilation at necropsy had no evidence of congestive heart failure and died in septic shock. One patient developed disseminated infection by *Mycobacterium avium-intracellulare*; sparse acid-fast bacilli surrounded by myocarditis were found in the heart at necropsy. Another patient died of sepsis due to *Pseudomonas aeruginosa*; however, neither culturable nor histologic evidence of microorganisms was found in the myocardium at necropsy. A third patient had sepsis due to *Staphylococcus aureus*; sparse gram-positive cocci were histologically identifiable within the myocardium at necropsy.

Discussion

Myocarditis: prevalence and etiology. Focal, mild and usually mononuclear myocarditis is a prevalent necropsy finding in patients dying from AIDS, occurring in 37 (52%) of 71 cases in our study. In general, the mild degree of inflammatory response in AIDS-associated myocarditis has been documented for most infectious lesions in these patients at necropsy and is believed to result from a severe deficiency of cell-mediated immunity and variable impairment of humoral immunity in their terminal course (13,14). Myocardial opportunistic pathogens could account for 7 of the 37 cases of myocarditis and were present in 2 cases

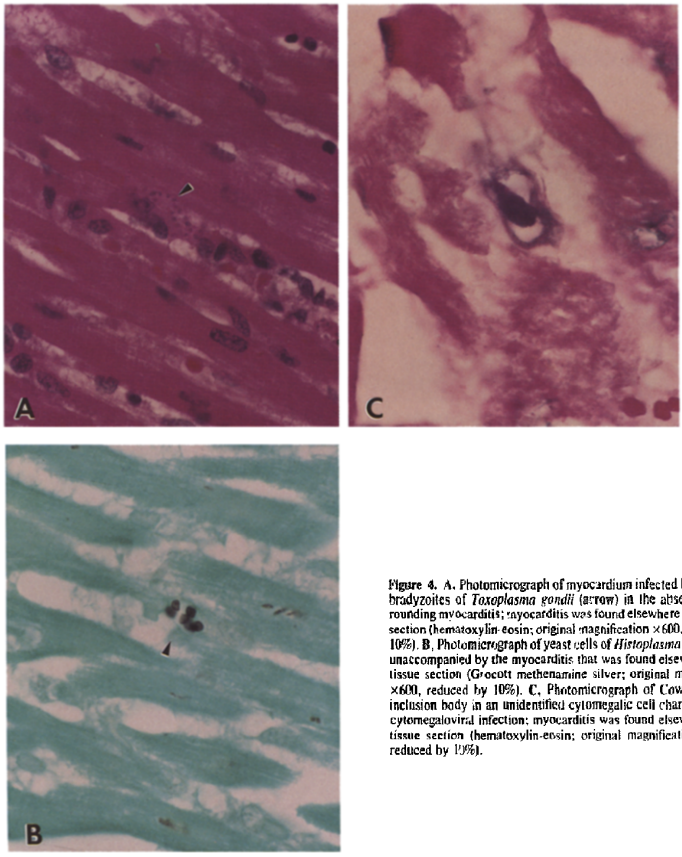

Figure 4. A, Photomicrograph of myocardium infected by encysted bradyzoites of *Toxoplasma gondii* (arrow) in the absence of surrounding myocarditis; myocarditis was found elsewhere in the tissue section (hematoxylin-eosin; original magnification ×600, reduced by 10%). B, Photomicrograph of yeast cells of *Histoplasma capsulatum* unaccompanied by the myocarditis that was found elsewhere in the tissue section (Grocott methenamine silver; original magnification ×600, reduced by 10%). C, Photomicrograph of Cowdry type A inclusion body in an unidentified cytomegalic cell characteristic of cytomegalovirus infection; myocarditis was found elsewhere in the tissue section (hematoxylin-eosin; original magnification ×1,000, reduced by 10%).

without myocarditis. In contrast, the etiology of myocarditis in most cases (30 cases [42%]) remains unclear.

The myocarditis found in most patients with AIDS in this study appeared histologically suggestive of viral infection. We found no clinical or histologic evidence for toxic, hypersensitivity or drug therapy-related causes. The possible

causes of viral myocarditis in these patients are potentially diverse. Cytomegaloviral infection of lung or adrenal gland usually reflects systemic infection in patients with AIDS (15) and occurred in 28 of the 37 myocarditis cases. Although not statistically associated with myocarditis or biventricular dilation in this study, cytomegalovirus represents a possible causative agent for some of these lesions (16,17). Intranuclear inclusions characteristic of cytomegaloviral infection were seen in the myocardium of only two patients; however, studies (18) utilizing in situ DNA hybridization techniques indicate that many infected cells, including myocytes, may not manifest characteristic inclusion bodies. In contrast, infection with Coxsackie B virus is the most common known cause of non-AIDS myocarditis in the United States and exhibits no viral-specific histologic finding (19,20). Finally, the human immunodeficiency virus itself may inflict damage on myocytes either by direct cytolytic infection or by means of a mechanism of "innocent bystander destruction" proposed by Ho et al. (21) for neuroglial cell damage in AIDs-associated subacute encephalitis. According to this hypothesis, human immunodeficiency virus replication within interstitial lymphocytes and macrophages would release enzymes that were toxic to parenchymal cells, in this case myocytes. Viral cultures of myocardium were carried out in only six cases in our study and were uniformly negative. Clarification of the various possible viral causes of AIDS-associated myocarditis awaits application of nucleic acid probes for cytomegalovirus, Coxsackie B, human immunodeficiency virus and other clinically implicated viruses.

Microvascular spasm leading to focal chronic myocarditis has been recently described (22). It is possible that this process may account for some cases of myocarditis. Alternatively, patients with AIDS are known to manifest alterations in immune regulation such as immune-mediated thrombocytopenia (23,24) and an increased prevalence of drug reactions to sulfa compounds (25). Thus, humorally mediated autoimmune reactions as seen in myocarditis associated with antimyosin antibodies may be operative (26,27). In addition, myocyte-specific T suppressor/cytotoxic lymphocytes have been reported (28) to effect myocyte damage in viral myocarditis. Although AIDS patients exhibit both a qualitative and quantitative deficiency in specific and nonspecific cytotoxicity (29,30), immune cell typing of mononuclear inflammatory cells is necessary to further define these lesions.

Etiology of biventricular dilation. In our cases, cardiac pathologic features were most consistent with acute myocarditis as the cause of biventricular dilation at necropsy (that is, the extent of left ventricular dilation was moderate [mean transverse diameter 4.3 ± 0.4 cm] as compared with control hearts [mean transverse diameter 2.6 ± 0.6 cm], the heart weight was not consistently increased [>400 g] and histologic interstitial fibrosis was generally lacking). Although pathologic features of dilated cardiomyopathy including cardiomegaly and interstitial fibrosis were present in two cases reported earlier (8), the likelihood of an acute viral etiology seems considerable. Thus, in the four patients with biventricular dilation at necropsy for whom neither histologic nor culturable evidence of infectious myocardial pathogens could be demonstrated, we believe that ventricular dilation was most likely due to acute viral myocarditis. In contrast, bacterial myocarditis due to *S. aureus* or *M. avium intracellulare* was the likely cause of biventricular dilation found at necropsy in two patients who died from sepsis with the corresponding microorganism. The differential diagnosis of biventricular dilation in a patient with AIDS should, therefore, focus on myocarditis due to viral or other infectious microorganisms responsible for concomitant systemic infection.

Clinical implications. Heart failure associated with postmortem evidence of biventricular dilation contributed a small but significant cause of morbidity and mortality in our study patients (four cases [6%]). In comparison, respiratory failure as a consequence of chronic opportunistic pulmonary infection was the cause of death in 59% of patients in the present study and accounts for between 58 and 64% of the reported cumulative mortality in patients with AIDS (3,31). Several therapies have recently emerged that show promise in combating the infectious pulmonary complications of AIDS and prolonging median survival (32,33). As patients are more effectively managed with respect to their pulmonary disease, the morbidity and mortality due to cardiac disease may increase. The cases presented here suggest a need for early detection and supportive therapy for cardiac dysfunction in these patients.

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