Cytomegalovirus Pneumonitis in Patients with AIDS*
Findings in an Autopsy Series
Jeanne Marie Wallace, M.D., F.C.C.P.; and James Hannah, M.D.

Cytomegalovirus (CMV) pneumonitis is a common complication of AIDS. With the development of potentially effective drug therapy, the indications for treatment and best means of diagnosis have become issues of practical importance. We reviewed the clinical records and autopsy material from 54 patients dying with AIDS, 39 (72 percent) of whom had CMV infection documented postmortem by culture and the presence of inclusion bodies. Of the patients with CMV infection, disseminated disease was documented in 23 (50 percent) and pneumonitis in 31 (50 percent). Although the majority of patients with CMV pneumonitis had additional forms of pulmonary pathology, CMV was the only causative agent identified in two patients with severe pulmonary disease. Since CMV can cause severe lung damage and disseminated infection in patients with AIDS, specific treatment may be beneficial. Improved diagnostic technology is needed in this area.

Infection due to cytomegalovirus (CMV) is a well-recognized complication in patients with acquired immunodeficiency syndrome (AIDS). Although in the past there has been no effective treatment, more recently, potentially useful pharmacologic agents against CMV have been developed. Therefore, the detection of CMV infection has taken on practical importance in the care of patients with AIDS.

Serologic evidence of previous experience with CMV often can be found in normal adults, indicating that subclinical CMV infection commonly occurs in the normal population. In immunocompromised patients, CMV is often recovered from respiratory secretions or urine, although many of these patients have no symptoms. Thus, in addition to the detection of CMV, documentation of clinically significant disease would be essential to decisions regarding the need for treatment in an individual patient.

In reports of the pulmonary complications with AIDS, CMV has frequently been cultured from respiratory specimens. However, the contribution of CMV pneumonitis to morbidity and mortality in patients with AIDS has been questioned. Because documentation of clinically significant CMV infection is difficult during life, the pathologic effects in the lung may be elucidated by autopsy studies. Several autopsy series have confirmed the high frequency of CMV pneumonitis in patients with AIDS. In this study, we have correlated the pulmonary autopsy findings and antemortem clinical data from 54 patients dying with AIDS, 31 of whom had postmortem evidence of CMV pneumonitis. Our objectives were to (1) analyze the role of CMV infection in causing clinically significant pulmonary disease, and (2) assess the value of conventional diagnostic pulmonary techniques in AIDS patients with CMV pneumonitis.

METHODS

The autopsy records of all patients reported in the UCLA Medical Center Autopsy Registry to have died with AIDS between November 1981 and March 1985 were reviewed. Of the patients thus identified, 54 fulfilled the criteria for the diagnosis of AIDS established by the Centers for Disease Control and were included in the study. The abnormal gross findings and cause of death noted in each report was recorded.

For each patient, sections of lung, lymph nodes, spleen, adrenal, and other tissue indicated to be of interest in the autopsy record were examined. The number of hematoxylin and eosin (H-E) stained slides reviewed varied from two to 14 for lung tissue, and from three to 12 for extrapulmonary tissue. Gomori methanamine-silver (GMS), Gram, Ziehl-Neelsen (Z-N), and periodic acid-Schiff (PAS) stained lung sections were also reviewed.

The results of cultures taken during the autopsies were compiled from records available in the UCLA Clinical Microbiology Laboratory. Postmortem lung, adrenal, retina, bowel, spleen, liver, and lymph node tissue was cultured for viruses in human embryonic lung fibroblast, human foreskin fibroblast, and primary African green monkey kidney cell lines in the standard manner. The cultures were kept 35 days before being reported as negative. Examination for cytopathic effect was performed daily during the first week, and two to four times per week thereafter. Pulmonary tissue was also cultured...
for (1) aerobic bacteria (on blood, chocolate, and MacConkey's agar); (2) mycobacteria (on Lowenstein-Jensen and Wallenstein plates, and in Middlebrook 7H12 media); and (3) fungi (on Sabouraud's medium and inhibitory mold agar).

Autopsy evidence of CMV infection was considered to be present if (1) typical intranuclear or intracytoplasmic inclusionst were observed and (2) CMV was cultured from autopsy tissue obtained from at least one site. Of the 54 patients studied, 30 had autopsy evidence of CMV infection, and 31 had CMV pneumonitis.

The antemortem clinical and microbiologic records of all 54 patients were reviewed. Prior to death, 36 patients had been hospitalized at the UCLA Medical Center, and 18 at a Southern California Kaiser Permanente Facility. Cytomegalovirus complement fixation antibody titers were determined by a modified Lenette technique in which two units of hemolysin and a 100 percent end point were used. Antemortem microscopic specimens consisted of biopsy specimens which were fixed in formalin prior to sectioning for H and E, GMS, Z-N, and PAS stained slides and smears which were fixed in 95 percent ethanol fixative prior to Papanicolaou staining or air-dried prior to GMS, Gram, Z-N, and PAS staining. Antemortem specimens were cultured for viruses and other organisms in the same manner as above.

Demographic characteristics of each of the 39 patients with autopsy evidence of CMV infection were compared with those of the 15 patients in whom the infection was not demonstrated at autopsy. For each patient with CMV infection, postmortem data regarding the cause of death and sites of CMV infection were compiled. For those with CMV pneumonitis, the types of coexisting pulmonary disease and the associated histologic findings were examined. The severity of lung damage was correlated with the density of CMV inclusion bodies and whether the patient received mechanical ventilation before death. The proportion of patients who, before death, had either a CMV complement fixation antibody titer greater than 1:8 or CMV cultured from pulmonary and extrapulmonary specimens was examined. For those with positive antemortem cultures, the time interval between collection of each specimen and the first observation of cytopathic effect in culture was correlated with whether autopsy evidence of CMV infection was present. The diagnostic yield of sputum collection, fiberoptic bronchoscopy (FOB), and diagnostic thoracotomy for each of the 31 patients with autopsy evidence of CMV pneumonitis was determined. During FOB, bronchial washings, brushings and fluoroscopically-guided transbronchial biopsy specimens were obtained. Bronchoalveolar lavage was performed during 12 FOB procedures. Only pulmonary specimens in which typical CMV inclusion bodies could be demonstrated were considered diagnostic of pulmonary infection.

Statistical calculations were performed using chi-square analysis or two-sided Student's t-tests in which the variances were pooled. A p value less than 0.05 was considered significant. Data are expressed as mean value ± SEM.

RESULTS

Demographic Characteristics

The age at the time of death of the 39 patients with autopsy evidence of CMV infection, 39.3 ± 1.7 years, was the same as that of the 15 patients in whom CMV infection was not documented at autopsy, 37.5 ± 2.6 years. There was no significant difference in the racial background between the patients with and without CMV infection. All 39 patients had at least one identifiable risk factor for the development of AIDS: 37 had a history of homosexual lifestyle; five were illicit intravenous drug users; two had received blood transfusions within five years prior to the time that AIDS was diagnosed; and one was a recent immigrant from Haiti. The frequency of each risk factor among the patients with and without autopsy evidence of infection did not differ significantly. Kaposi's sarcoma was demonstrated during the autopsy examination in 21 of the patients with CMV infection, but the incidence was not statistically different. There was no significant difference in the period from the time AIDS was diagnosed until death between the group with (7.8 ± 0.85 months) and without (6.0 ± 1.9 months) CMV infection documented at autopsy.

Autopsy Findings

Respiratory failure was considered a major cause of death in 31 (80 percent) of the patients with autopsy evidence of CMV infection. In 14, overwhelming infection was the major factor contributing to death. The responsible organisms were: CMV (two cases); CMV and Mycobacterium avium-intracellulare (eight cases); CMV and Cryptococcus neoformans (two cases); and Gram-negative bacilli (two cases). Compared to the 15 patients without evidence of CMV infection autopsied during the same time period, there was no significant difference in the frequency of any cause of death.

Table 1 shows the sites of tissue involvement with inclusion bodies in the 39 patients found to have CMV infection at autopsy. The lung was the site most frequently affected; and in 11 patients (28 percent), it was the only site of involvement. Of the 28 patients with extrapulmonary disease, five (18 percent) had one; nine (32 percent) had two; three (11 percent) had three; and 11 (39 percent) had more than three sites of involvement. The adrenals were the most frequent extrapulmonary site of CMV infection (28 patients); and in four patients, they were the only site in which CMV inclusion bearing cells could be demonstrated. Evidence of CMV infection of the retina was found in 16 patients; and in 11 patients, involvement of the gastrointestinal tract was noted. Typical cytopathic changes were also occasionally demonstrated in central nervous system, spleen hepatic, pancreatic, geni-

Table 1—Autopsy Tissue with CMV Inclusion Bodies in 39 Patients with AIDS and Cytomegalovirus Infection

<table>
<thead>
<tr>
<th>Site</th>
<th>No. of Patients</th>
<th>Site Involved (%)</th>
<th>Only Site Involved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>31 (80)</td>
<td>11 (28)</td>
<td></td>
</tr>
<tr>
<td>Adrenals</td>
<td>28 (72)</td>
<td>4 (10)</td>
<td></td>
</tr>
<tr>
<td>Retina</td>
<td>16 (41)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>11 (28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central nervous system</td>
<td>6 (15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spleen</td>
<td>4 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>4 (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>3 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genitourinary tract</td>
<td>3 (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>2 (5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CHEST / 22 / 2 / AUGUST, 1987 199

Downloaded From: http://journal.publications.chestnet.org/pdaccess.ashx?url=/data/journals/chest/21565/ on 06/25/2017
Cytomegalovirus

Figure 1. CMV pneumonitis with diffuse alveolar damage (H-E, original magnification × 100). Inset, CMV inclusion (H-E, original magnification × 400).

Of the 31 patients with CMV pneumonitis, 29 had coexisting pulmonary pathology documented at autopsy. Twenty-four patients had evidence of at least one additional active pulmonary infection including the following: Pneumocystis carinii (12 patients); M avium-intracellularare (eight patients); pyogenic bacteria (five patients); and C neoformans (three patients). Twelve patients had noninfectious pulmonary disease including Kaposi's sarcoma (ten patients) and thromboembolism (two patients). In two patients who died of respiratory failure due to severe widespread parenchymal disease, CMV was the only causative agent that could be identified.

The histologic features that were associated with pulmonary CMV infection are shown in Figures 1 and 2. Two histologic patterns were observed as follow: (1) diffuse alveolar damage (DAD); and (2) focal interstitial pneumonitis. Twenty-two patients had severe pathology due to DAD. Findings of both the exudative (interstitial edema and hyaline membranes) and the proliferative phase (regeneration of the alveolar epithelium, interstitial inflammation, and fibrosis) were noted in pulmonary tissue from these patients. Nine patients had focal interstitial pneumonitis characterized by focal mononuclear cell inflammation with or without interstitial fibrosis. There was no evidence of reactive pneumocytes in pulmonary tissue from these patients. Pulmonary damage associated with focal interstitial pneumonitis was mild to minimal.

Diagnostic cytomegalic cells with typical intranuclear and intracytoplasmic inclusion bodies were diffusely scattered throughout the lung tissue in patients with both histologic patterns. The CMV-infected cells were most frequently observed in the alveolar spaces, and appeared to line the alveolar epithelium. Necrotizing miliary lesions described in patients with CMV infection complicating bone marrow transplantation were not seen. In addition to pneumonitis, one patient had ulcerative tracheobronchitis due to CMV.

Figure 2. CMV inclusions with minimal alveolar damage (H-E, original magnification × 100). Inset, CMV inclusion (H-E, original magnification × 630).

Judged by the number of CMV inclusion-bearing cells, CMV infection of the lung parenchyma was scant in 15 patients and moderate to heavy in 16. Of the patients with scant infection, eight had severe DAD which was primarily attributed to P carinii infection in six and to CMV infection in two; and seven had focal interstitial pneumonitis attributed to CMV infection. Of the patients with moderate to heavy infection, 14 had severe DAD which was primarily attributed to CMV infection in eight and to CMV and P carinii infection in six; and two had focal interstitial pneumonitis attributed to CMV infection. Numerous cytomegalic cells and severe DAD were observed in both patients who had CMV pneumonitis without coexisting pathology.

Of the 31 patients found to have CMV pneumonitis at autopsy, 13 were given mechanical ventilatory support for one day to three months prior to death. The DAD was noted in 12 of these patients and focal interstitial pneumonitis in one. Of the 18 patients who did not require mechanical ventilation, ten had DAD and eight had focal interstitial pneumonitis.

Table 2—Correlation of Antemortem Cytomegalovirus Cultures with the Presence of CMV Inclusion Bodies in Autopsy Tissue

<table>
<thead>
<tr>
<th>Specimen Cultured</th>
<th>Patients with CMV Inclusion Bodies in Pulmonary Tissue</th>
<th>Patients with CMV Inclusion Bodies in Extrapulmonary Inclusion Bodies in Tissue only</th>
<th>Patients with CMV no Autopsy Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 31</td>
<td>N = 8</td>
<td>N = 15</td>
</tr>
<tr>
<td>Sputum</td>
<td>3/19 (16%)</td>
<td>0/3 (0%)</td>
<td>1/7 (14%)</td>
</tr>
<tr>
<td>Bronchoscopy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>specimens</td>
<td>10/20 (50%)</td>
<td>4/5 (80%)</td>
<td>1/3 (33%)</td>
</tr>
<tr>
<td>Blood</td>
<td>9/16 (56%)</td>
<td>2/4 (50%)</td>
<td>1/7 (14%)</td>
</tr>
<tr>
<td>Urine</td>
<td>17/25 (68%)</td>
<td>4/6 (67%)</td>
<td>5/8 (63%)</td>
</tr>
<tr>
<td>Semen</td>
<td>7/12 (55%)</td>
<td>1/2 (50%)</td>
<td>3/5 (60%)</td>
</tr>
</tbody>
</table>

Cytomegalovirus Pneumonitis in AIDS Patients (Wallace, Hannah)
Table 3—CMV Complement Fixation Antibody Titers in Patients with and Without CMV Inclusion Bodies in Autopsy Tissue

<table>
<thead>
<tr>
<th>Autopsy Tissue with CMV Inclusion Bodies</th>
<th>No. Patients with Complement Fixation Antibody Titer*</th>
<th>Anti-complementary</th>
<th>Not Done</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary (N=31)</td>
<td>24</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Extrapulmonary only (N=8)</td>
<td>7</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>None (N=15)</td>
<td>10</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Performed within six months prior to death.
†A titer >1.8 was considered positive.

Correlation of Autopsy Findings with Results of Antemortem Diagnostic Evaluations

Table 2 shows the results of antemortem CMV cultures performed within two months prior to death from patients found to have CMV inclusion bodies in pulmonary tissue, extrapulmonary tissue only or no tissue at autopsy. There was no significant difference in the frequency with which CMV was isolated from any of the types of specimens cultured among the three groups. For the majority of patients who had inclusion bodies in pulmonary autopsy tissue, the time between collection of respiratory specimens and detection in culture was less than two weeks. In contrast, demonstration of the typical cytopathic effect in all respiratory cultures from patients without autopsy evidence of CMV pneumonitis required greater than two weeks. There was no correlation between the time to positive culture of respiratory specimens and the severity of pulmonary pathology.

The CMV complement fixation antibody titers for the patients who at autopsy had inclusion bodies in pulmonary tissue, extrapulmonary tissue only, and no tissue are shown in Table 3. All CMV complement fixation antibody tests were performed within six months prior to death. In five patients with pneumonitis and one with extrapulmonary infection, negative complement fixation antibody titers were obtained within two weeks prior to death, at a time when the patient was critically ill. There was no significant difference in the number of patients who had positive or negative complement fixation tests in each of the three groups.

The diagnostic yield of all pulmonary procedures performed within one month prior to death in the 31 patients with inclusion bodies in pulmonary autopsy tissue is shown in Table 4. In no case was a sputum sample diagnostic. The diagnostic yield for FOB was three of 20 procedures (15 percent). The positive specimens included bronchial washings (one patient), bronchial washings and brushings (one patient), and bronchoalveolar lavage (one patient). Only one of seven diagnostic thoracotomy specimens demonstrated the typical cytopathic changes of CMV infection, although in three, the organism was isolated in culture.

Discussion

Cytomegalovirus is a frequently encountered pathogen in patients with AIDS. Although in the past, CMV infection has been considered an untreatable complication, several recent reports have demonstrated advances toward the development of a more effective therapeutic agent. Preliminary studies have suggested that anti-CMV therapy is more promising in patients with retinitis and gastrointestinal infection than in those with pneumonitis. Explanations for this observation have included overestimation of the role of CMV in causing lung damage or the presence of advanced disease by the time the pulmonary infection was recognized and treated. Thus, the potential for treating CMV infection has raised two issues. First, is CMV infection of the lung a clinically significant process justifying specific antiviral therapy? Second, if so, do conventional pulmonary diagnostic techniques provide sufficiently sensitive and early detection of CMV pneumonitis for initiation of an optimal treatment program?

The experience reported here confirms the high frequency of pulmonary involvement in AIDS patients with CMV infection. In our series, the lung was the most frequent site of CMV infection; and in almost one third of our patients, it was the only tissue in which inclusion bodies were found at autopsy. Respiratory failure was the leading cause of death among the patients with CMV infection. Severe CMV pneumonitis leading to respiratory failure and death has been documented in renal and bone marrow transplant recipients. Because coexisting forms of pulmonary pathology are usually present, the role of CMV pneumonitis in causing morbidity and mortality in patients with AIDS has been questioned. The majority of our patients did have one to three coexisting pathologic processes, making it difficult to precisely define the role of CMV in causing clinically significant disease. However, in two patients who died of respiratory failure due to severe widespread pulmonary disease, CMV was the only identifiable pathogen. In addition, regardless of the type and extent of coexisting disease,
a high density of inclusion bodies was associated with severe lung damage. These observations indicate that CMV pneumonitis is a common cause of severe pulmonary disease in patients with AIDS.

Besides causing lung damage, our data suggest that CMV can cause morbidity and mortality in patients with AIDS by disseminated infection. Over one half of our patients with CMV infection had involvement of two or more sites; and in 14, overwhelming CMV infection was considered a major factor leading to death. Thus, evidence of respiratory impairment or disseminated disease would be indication for treatment in patients with AIDS and CMV pneumonitis.

Two distinct histologic patterns were noted in pulmonary autopsy tissue involved with CMV pneumonitis—(I) DAD, and (2) focal interstitial pneumonitis. Diffuse alveolar damage was observed in 22 patients (71 percent). It was attributed to pulmonary infection with CMV in ten patients, and both P carinii and CMV in 12. The histologic findings of DAD represent a nonspecific reaction to a variety of insults which cause alveolar epithelial and endothelial injury.7 Mechanical ventilation may have contributed to the development of DAD in 12 of our patients with CMV pneumonitis; however, it was never instituted in ten others with identical histologic findings. Both patients found to have CMV as the only pulmonary pathogen had DAD. In only one could the effect of mechanical ventilation have contributed to the pathologic findings.

Focal interstitial pneumonitis was the predominant histologic pattern associated with CMV pneumonitis in nine (29 percent) of our patients. In general, the patients with focal interstitial pneumonitis had mild to minimal lung damage. Thus, although CMV infection can cause severe pulmonary damage resulting in respiratory failure and death, it may also be associated with relatively mild pulmonary pathology, the clinical significance of which is unknown. It is unclear if the spectrum of pathologic findings is related to variations in individual pulmonary host response to CMV infection, or if the presence of focal interstitial pneumonitis represents earlier disease. Thus, pathologic criteria for treatment with drugs potentially effective against CMV in patients with less severe lung damage remain to be determined. Further information on the mechanisms of lung injury due to CMV infection would be useful as the indications for pharmacologic intervention are established.

Our study confirms that clinically significant CMV infection is difficult to distinguish from previous or subclinical infection in patients with AIDS. Most of our patients had positive CMV complement fixation titers regardless of whether CMV infection was documented at autopsy. In addition, the frequency with which CMV was isolated antemortem from respiratory specimens was not statistically different among patients who, at autopsy, had CMV inclusion bodies in pulmonary tissue, extrapulmonary tissue only, or no tissue. Our data did suggest that early detection of CMV in respiratory cultures was associated with cytopathic evidence of the infection in the lung. There was, however, no correlation between the time to positive culture of respiratory specimens and severity of pulmonary pathology demonstrated at autopsy. Therefore, the significance of culturing CMV from respiratory specimens without the demonstration of specific tissue pathology is uncertain, particularly in terms of decisions regarding the need for therapeutic intervention.

We have considered the presence of pathognomonic cells with intranuclear or intracytoplasmic inclusions to be a necessary criterion for the diagnosis of CMV pneumonitis. Unfortunately, using that criterion, the diagnostic yield of all pulmonary procedures performed in this study was extremely low. Cytomegalovirus pneumonitis was diagnosed prior to death in only four of our patients, probably due to inadequate sampling by the diagnostic techniques used, and lack of sensitive detection of CMV infected cells in the respiratory samples provided. Since CMV inclusions are most frequently seen in alveolar epithelial cells and alveolar macrophages, bronchoalveolar lavage has been suggested to be a useful technique for diagnosing CMV pneumonitis.22 Only 12 of our patients underwent bronchoalveolar lavage, and typical cytomegalic cells were demonstrated in one. The use of monoclonal antibodies and CMV-specific DNA probes have shown promise as more sensitive and specific tools for detecting CMV infected cells.22,23 Recently, detection of CMV infected cells in bronchoalveolar lavage specimens via an indirect immunofluorescence assay using CMV-specific monoclonal antibodies has been shown to be a sensitive and rapid method for the diagnosis of CMV pneumonitis.23 These newer techniques could greatly enhance the accuracy with which CMV pneumonitis is diagnosed in patients with AIDS.

We conclude that pulmonary CMV infection can cause significant pulmonary damage leading to respiratory failure and death in patients with AIDS. Thus, once effective treatment is available, it would be warranted in at least some cases. However, because some may have minimal associated pulmonary pathology, it is not clear if the risks of therapy would be warranted in all AIDS patients with CMV pneumonitis. Improved modalities for diagnosing CMV pneumonitis are needed. Even with the development of more sensitive and specific diagnostic techniques, decisions regarding the need for therapeutic intervention must be influenced by clinical factors such as the degree of respiratory impairment, and the overall clinical status of the individual patient, because these
factors will condition the clinical significance of pulmonary infection with CMV at a given point in time.

ACKNOWLEDGMENTS: The authors thank Dr. I. Jeffrey Strumpf for his help in obtaining clinical information on the patients treated in the Southern California Kaiser Permanente system.

REFERENCES