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Cytomegalovirus

An Unexpected Cause of Ventilator-associated Pneumonia

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Background: Cytomegalovirus (CMV) frequently is observed in immunocompromised hosts. The aim of this study was to report cases of ventilator-associated CMV pneumonia diagnosed by pathologic examination in intensive care patients without acquired immunodeficiency syndrome or hematologic malignancy or who were not receiving immunosuppressive agents.

Methods: From June 1, 1989, to May 31, 1994, 2,785 patients were hospitalized. During the study period, 60 autopsies and 26 open-lung biopsies were performed in nonimmunocompromised patients who were seen with acute respiratory failure and/or symptoms suggestive of ventilator-associated pneumonia. Cytomegalovirus pneumonia was diagnosed using pulmonary samples by the identification of large cells with large nuclei containing a basophilic or eosinophilic inclusion surrounded by a light halo. These typical findings always were associated with a diffuse interstitial pneumonitis.

Results: Cytomegalovirus pneumonia was diagnosed after histologic examination in 25 patients. The reason for admission to the intensive care unit was major surgery in 13 patients and medical problems in 12 patients. Ventilator-associated CMV pneumonia was diagnosed by histologic examination 22.4 ± 8.8 days after admission to the intensive care unit (median 18 days; range 10–40 days). The clinical description was similar with the 25 patients who were seen with ventilator-associated CMV pneumonia and the 61 patients without ventilator-asso-

ciated CMV pneumonia. However, there was a more severe hypoxemia (72 ± 16 vs. 95 ± 41 mmHg, $P < 0.05$) and a higher Weinberg's radiologic score (9.2 ± 1.9 vs. 7.4 ± 2.7 , $P < 0.05$) in the ventilator-associated CMV pneumonia group. Diagnosis of ventilator-associated CMV pneumonia was made for 9 of 17 patients when shell-vial culture technique using fluorescein-labeled antibody E 13 was performed on bronchoalveolar lavage products. Four of the eight patients treated by ganciclovir therapy died of multiple organ dysfunction syndrome.

Conclusions: The diagnosis of ventilator-associated CMV pneumonia should not be excluded in intensive care patients, even those without acquired immunodeficiency syndrome, hematologic malignancy, or immunosuppressive agents on admission. (Key words: Complications: cytomegalovirus; pneumonia. Lavage: bronchoalveolar. Ventilation: mechanical.)

MOST adults have been infected by cytomegalovirus (CMV), as shown by the presence of detectable antibodies. Furthermore, this CMV infection remains latent. When cell-mediated immunity is depressed, for example, in renal transplant patients receiving immunosuppressant drugs, reactivation of endogenous CMV is common and may produce clinical infection. Cell-mediated immunity also is reduced in other surgical patients,¹ particularly those who are critically ill with serious postoperative complications or those who have multiple injuries.² Until recently, CMV pneumonia was thought to be a rare but fatal illness, occurring primarily in immunocompromised hosts. Numerous viruses currently are considered nosocomial pathogens,³ but the importance of these agents compared with other pathogens has not been clearly defined, especially in adult patients in whom the lungs are mechanically ventilated. The aim of this study was to report a series of ventilator-associated CMV pneumonia diagnosed by histopathologic examination.

Materials and Methods

This study was conducted in our 15-bed medico-surgical intensive care unit (ICU) from June 1, 1989

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Lung Biopsy Sampling

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to May 31, 1994 and was approved by the local Committee for the Protection of Human Subjects. Autopsies were performed on patients who died with acute respiratory failure and/or symptoms suggestive of ventilator-associated pneumonia (VAP) with negative antemortem bacteriologic cultures (protected specimen brush, bronchoalveolar lavage, blind bronchial sampling). Open-lung biopsy was performed when a patient's respiratory status was worsening but bacteriologic cultures were negative (protected specimen brush, bronchoalveolar lavage, blind bronchial sampling) and no explanation for the impaired respiratory status could be found. Ventilator-associated CMV pneumonia was diagnosed when these two criteria were met: (1) mechanical ventilation for at least 7 days; (2) histologically proven CMV pneumonia. This delay virtually guaranteed that all patients with histologically proven CMV pneumonia were classified as such. Immunocompromised hosts were excluded from the study. Patients were classified as immunocompromised if there was an established diagnosis of immunodeficiency (*i.e.*, acquired immunodeficiency syndrome), or if the patient was receiving immunosuppressive agents for an underlying medical problem (*i.e.*, lymphoma, prior organ transplantation, *etc.*). Patients receiving steroids were also considered to be immunocompromised.⁴ The following data were prospectively recorded by a single physician: age; sex; Acute Physiology and Chronic Health Evaluation II score on admission⁵; hemoglobin; white blood cell differential count; presence of atypical lymphocytosis; serum concentrations of creatinine, bilirubin, aspartate aminotransferase, and alanine aminotransferase; maximal abnormalities on the chest roentgenogram using Weinberg's radiologic score⁶; underlying diagnoses; use of 5.0 mg · kg⁻¹ ganciclovir (Cytovene, Syntex Pharmaceuticals, Palo Alto, CA) twice a day for at least 2 weeks; duration of mechanical ventilation; duration of hospitalization; and final outcome.

Lung Biopsy Sampling and Processing

Histologic assessment was performed on pulmonary specimens obtained by open-lung biopsy or post-mortem histologic examination of the whole lung. In such cases, four or more biopsy specimens from each lobe were taken for histologic examination. They were fixed in 10% buffered formalin for 24 h at room temperature. Then samples were dehydrated in a modified alcohol series: 95% for 15 min, 100%

for 15 min, and xylene for 15 min. After dehydration, samples were embedded in a single paraffin block and serially cut to 4- μ m thick with standard microtomes with disposable blades. Slides were stained with hematoxylin-eosin-safran. Cytomegalovirus pneumonia was diagnosed on pulmonary samples by the identification of large cells with large nuclei containing a basophilic or eosinophilic inclusion surrounded by a light halo.^{7,8} Multiple cytoplasmic granular inclusions were often present. These typical findings were always associated with a diffuse interstitial pneumonitis characterized by the presence of inflammatory cells (predominantly lymphocytes), thickened alveolar septi, and an interstitial inflammation. A fibrinous alveolitis and a mild or moderate fibrosis were often associated. Bacterial pneumonia was defined by the presence of scattered neutrophilic infiltrates localized to terminal bronchioles and surrounding alveoli with evident confluence of infiltrates between adjacent lobules.^{9,10} Bacteriologic investigation was performed on open-lung biopsy or autopsy and included Gram and Ziehl-Neelsen staining and culture for bacteria, mycobacteria, and fungi.

Serologic Status: Viral Cultures

The CMV antibody status of patients was determined on admission to the ICU by an enzyme-linked immunosorbent assay (Behring, Marburg, Germany). Bronchoalveolar lavage (BAL), blood, or urine cultures were performed when the diagnosis of CMV pneumonia was suspected clinically. Bronchoalveolar lavage was performed by wedging the bronchoscope into a subsegment of the area with greatest radiologic abnormality, or when disease was diffuse, into the lingula or right middle lobe. Normal saline was sequentially instilled in 20-ml aliquots (total, to 100 ml) and suctioned into sterile traps. The first aliquot was discarded. Bronchoalveolar lavage specimens were sent for conventional microbiologic processing. In addition, BAL, blood, and urine samples were sent for shell-vial culture technique. Specimens for these cultures were inoculated onto MRC-5 cells in tissue culture.¹¹ Monoclonal antibodies directed against immediate early antigen (E 13, Biosoft, Clonatec, Paris) were applied 48 h after inoculation for detection of viral antigen expression.¹² Only BAL, blood, and urine cultures performed within a 1-week period preceding histologic assessment were considered.

Results

Histologic Diagnosis of Ventilator-associated Cytomegalovirus Pneumonia

There were 2,785 admissions to the ICU during the study period. During this period, 60 autopsies and 26 open-lung biopsies were performed in nonimmunocompromised patients. In all, we observed 25 cases of CMV pneumonia diagnosed by histologic examination (fig. 1). In the remaining 61 cases, no histologic sign of CMV pneumonia was observed. Ventilator-associated CMV pneumonia was diagnosed by histologic examination 22.4 ± 8.8 days after ICU admission (median, 18 days; range, 10–40 days). Seventeen of these cases of CMV pneumonia were diagnosed on autopsy and eight cases by open-lung biopsy. Histologic examination showed that CMV was the sole respiratory pathogen in 88% of the cases. In three patients, lung cultures were positive with one microorganism (*Staphylococcus aureus*, *Serratia marcescens*, and *Streptococcus pneumoniae*) and histologic results were consistent with a bacterial pneumonia associated with the CMV pneumonia.

Diagnostic Performance of the Various Testing Methods Used to Diagnose Ventilator-associated Cytomegalovirus Pneumonia

Patient serologic status was determined in 18 cases. Thirteen of these 18 patients were seropositive for CMV on admission to the ICU. During the same study period, 58% of the 2,785 patients admitted to the ICU were seropositive for CMV. Bronchoalveolar lavage was performed in 17 of the 25 study patients whereas blood and urine cultures were performed in 15 of the 25 study patients. Bronchoalveolar lavage, blood, and urine cultures were performed during the week preceding histologic assessment in 43 of the 61 patients without histologic signs of CMV pneumonia. The sensitivity of BAL, blood, and urine cultures for the diagnosis of histologically proven ventilator-associated CMV pneumonia was 53%, 20%, and 13%, respectively. The specificity of these tests for the diagnosis of histologically proven ventilator-associated CMV pneumonia was 92%, 83%, and 62%, respectively.

Comparison of Clinical Presentation of Ventilator-associated Cytomegalovirus Pneumonia with Patients without Cytomegalovirus Pneumonia

Characteristics of the 25 patients with ventilator-associated CMV pneumonia are outlined in table 1.

The onset of the clinical deterioration of respiratory status occurred at 17.4 ± 8.8 days after ICU admission (median, 14 days; range, 8–38 days). The presence of fever $>38^\circ\text{C}$ was observed in all but 6 patients (mean, 38.5°C ; range, 37.0 – 40.1°C). Chest roentgenograms did not show any specific signs; Weinberg's score was 9.2 ± 1.9 (median, 9; range, 4–12). Evidence of CMV infection of the retina was never found. Involvement of the gastrointestinal tract was noted in one of the 25 patients with CMV pneumonia. At the moment of diagnosis of CMV pneumonia, the minute ventilation used was $13.2 \pm 3.0 \text{ l} \cdot \text{min}^{-1}$ (range, 9.0–20.0), and the highest FIO₂ used was 0.68 ± 0.17 (range, 0.45–1.0). All patients were ventilated with positive end-expiratory pressure. Laboratory data are summarized in table 2. Hypoxemia and moderate hypercapnia were observed on arterial blood gases at the moment of diagnosis of VAP. The CD4+:CD8+ ratio was assessed in 17 patients and was found reversed in 5 of them.

Comparison of the 25 patients with VAP and the 61 patients without histologic sign of CMV pneumonia showed a more severe hypoxemia in the CMV group ($72 \pm 16 \text{ mmHg}$ vs. $95 \pm 41 \text{ mmHg}$, $P < 0.05$) and a higher Weinberg's score (9.2 ± 1.9 vs. 7.4 ± 2.7 , $P < 0.05$) whereas age, Acute Physiology and Chronic Health Evaluation II score on admission, duration of mechanical ventilation, PaCO₂, white blood cell count, and temperature were not statistically different.

Evolution of the Respiratory Status of the Treated Patients

Only the eight patients who underwent open-lung biopsy were treated with ganciclovir for their ventilator-associated CMV pneumonia (table 3). The pulmonary status of four of these eight patients was improved within the first 5 days after the onset of ganciclovir therapy permitting an increase of more than 75% of their PaO₂/FIO₂ ratio. Of the four patients who died, we observed an initial good response to antiviral therapy in two cases, with an increase of the PaO₂/FIO₂ ratio of 25–30%.

Discussion

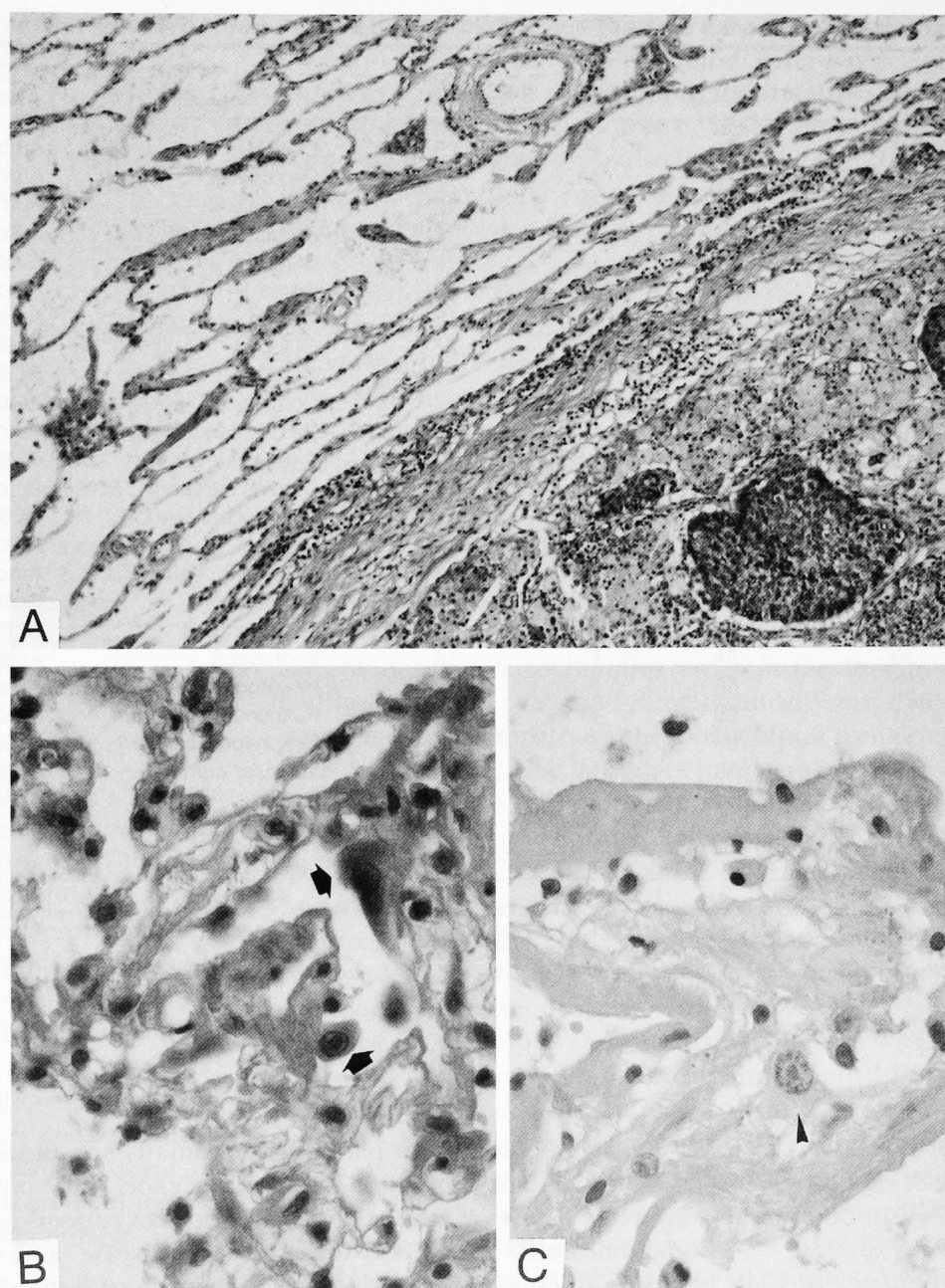
Cytomegalovirus Pneumonia and Mechanical Ventilation

The purpose of this study was to describe and elaborate on the previously unreported problem of venti-

Fig. 1. Patient 18. (A) Surgi- men from a right upper lo- Lobular adenocarcinoma a- surrounded by healthy pan- (magnification $\times 250$, hem- eosin-safran stain). (B) Ope- opsy on day 37 after surge- megalovirus pneumonia v- cells with large nuclei con- inclusion surrounded by a- (arrows) associated with- ence of inflammatory cells- cation $\times 400$, hematexylin- ran stain). (C) Postmorte- nation on day 51 after- Cytomegalovirus pneumo- large cells with large nuclei- ing an inclusion surround- light halo (arrow) associat- presence of inflammatory- thickened alveolar septi w- fibrosis, and hyaline m- (magnification $\times 400$, hem- eosin-safran stain).

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Fig. 1. Patient 18. (A) Surgical specimen from a right upper lobectomy. Lobular adenocarcinoma associated surrounded by healthy parenchyma (magnification $\times 250$, hematoxylin-eosin-safran stain). **(B)** Open-lung biopsy on day 37 after surgery. Cytomegalovirus pneumonitis with large cells with large nuclei containing an inclusion surrounded by a light halo (arrows) associated with the presence of inflammatory cells (magnification $\times 400$, hematoxylin-eosin-safran stain). **(C)** Postmortem examination on day 51 after surgery. Cytomegalovirus pneumonitis with large cells with large nuclei containing an inclusion surrounded by a light halo (arrow) associated with the presence of inflammatory cells, thickened alveolar septi with septal fibrosis, and hyaline membranes (magnification $\times 400$, hematoxylin-eosin-safran stain).



lulator-associated CMV pneumonia in the ICU. We used histologic signs, the "gold standard," for the diagnosis of CMV pneumonia. According to the literature, histologic examination has proved to be a highly specific tool for the diagnosis of CMV pneumonia.^{11,13-15} In fact, CMV induces highly specific cytologic modifications (*i.e.* cytomegaly, intranuclear inclusions, intracytoplasmic inclusions) that are totally different from those produced by other Herpesviridae.^{16,17} We considered the presence of pathognomonic cells with intranuclear

inclusions to be a necessary criterion for the diagnosis of CMV pneumonia. From a practical point of view, it would appear necessary to examine several sections because cytologically altered cells are present only in some sections. Distribution of infected cells within a tissue may be highly variable, thus reducing the chance of finding them in a given section.

Oda *et al.*¹⁸ have noted that CMV pneumonia could be observed in patients without hematologic malignancies or acquired immunodeficiency syndrome. They

Table 1. Characteristics of the 25 Patients with Ventilator-associated Cytomegalovirus Pneumonia

Patient No.	Age (yr)	Sex	APACHE II on Admission	Diagnosis	OLB/ Autopsy	Mechanical Ventilation (days)*	Blood Transfusion†
1	66	F	25	COLD‡	Autopsy	14	Yes
2	76	M	17	Peritonitis§	Autopsy	42	Yes
3	72	M	16	Peritonitis§	Autopsy	22	Yes
4	82	M	18	Cardiac surgery§	Autopsy	34	Yes
5	69	M	12	COLD§	Autopsy	15	Yes
6	77	M	22	Coma	Autopsy	22	Yes
7	67	M	16	COLD‡	Autopsy	29	Yes
8	72	F	27	COLD‡	OLB	8	Yes
9	78	M	20	COLD‡	OLB	7	Yes
10	71	F	17	Coma	Autopsy	16	Yes
11	76	F	29	Gastric cancer§	Autopsy	14	Yes
12	67	M	13	Cardiac surgery§	OLB	17	Yes
13	54	M	14	Cardiac surgery§	Autopsy	7	Yes
14	53	M	12	Esophageal cancer§	OLB	26	No
15	75	F	29	Coma	Autopsy	17	No
16	71	F	31	Meningitis	Autopsy	15	No
17	49	F	21	Myocarditis	OLB	31	No
18	72	M	15	Lung cancer§	OLB	37	Yes
19	84	F	18	Peritonitis§	Autopsy	13	Yes
20	68	F	23	Hepatocarcinoma§	Autopsy	10	Yes
21	65	M	35	Pulmonary embolism	Autopsy	36	Yes
22	63	F	15	Esophageal cancer§	OLB	20	No
23	65	M	20	Vascular surgery§	OLB	31	Yes
24	54	F	30	Coma	Autopsy	10	Yes
25	62	M	17	Lung cancer§	Autopsy	7	No
Mean ± SD	68.3 ± 9.2		20.5 ± 6.5			20.0 ± 10.5	

OLB = open lung biopsy; APACHE II = Acute Physiology and Chronic Health Evaluation score; COLD = chronic obstructive lung disease.

Duration of mechanical ventilation before OLB or autopsy.

† Blood transfusions from unrelated volunteers unscreened for CMV received before the development of CMV pneumonia.

‡ Acute exacerbation of COLD.

§ Major surgery.

also observed histologic CMV pneumonia in patients with cancer. In most cases, documented infection with CMV in nonimmunosuppressed hosts produces little, if any, disease.¹⁹ Although one could consider that the frequency of CMV infection fluctuates depending on immunologic disturbances observed in ICU patients, we were unable to find any published data on the incidence of CMV pneumonia in mechanically ventilated patients. It is noteworthy that ICU patients are considered hosts susceptible to bacterial or fungal infections (linked to impaired host defenses) but not viral infections. The absence of previous publications on the existence of ventilator-associated CMV pneumonia may reflect the lack of a standardized approach to the documentation of CMV pneumonia. Our diagnostic approach, which uses frequent virologic assessment of blood, urine and BAL fluid, suggests that CMV pneu-

monia is not an exceptional cause of VAP. In our experience, CMV pneumonia could develop in all categories of patients (multiple trauma, chronic obstructive lung disease, and surgical patients). It must be noted that the true incidence of CMV pneumonia could not be drawn from our study. Indeed, open-lung biopsy and autopsies were performed essentially to locate the cause of a respiratory failure when all bacteriologic cultures were negative. Indirect findings suggest that CMV infection could play an important role in the morbidity and mortality of ICU patients. For example, Domart *et al.*²⁰ have shown that, in patients with mediastinitis after cardiac surgery, mortality was higher for patients with viral shedding than for patients without it.

The mechanisms of acquisition of CMV pneumonia during ICU stays remain unknown. Human CMV is

Table 2. Laboratory Abnormalities in Ventilator-Associated Cytomegalovirus Pneumonia

Leukocyte count (g · L ⁻¹)
Neutrophils (%)
Lymphocytes (%)
Mononucleosis picture of the peripheral blood smear
Hemoglobin (g/dl)
Thrombocyte count (g · L ⁻¹)
P _a O ₂ (mmHg)
P _a O ₂ /F _i O ₂ (mmHg)
P _a CO ₂ (mmHg)
ASAT
> 2× normal
ALAT
> 2× normal
Serum bilirubin (μmol/l)
> 1.5 × normal
Serum creatinine (μmol/l)
> 120 μmol/l

Values are mean ± SD (range).

ASAT = aspartate aminotransferase; ALAT = alanine aminotransferase.

thought to infect 70% of asymptomatic and silent, and produce lesions in any host. There is also a growing evidence for nosocomial transmission of CMV in patients, with the risk of acquisition to the number of transfused blood products. This possibility stresses the importance of screening for CMV infection before and after contact with environmental objects potentially infected secretions.

Clinical and Radiologic Findings in Ventilator-Associated Cytomegalovirus Pneumonia

We found that clinical findings differentiating CMV from bacterial pneumonia were noted, however, that the diagnosis was often delayed after a long duration of mechanical ventilation (median, 18 days) as reported in the literature. CMV pneumonia played only a small role in the diagnosis of CMV pneumonia. All ICU patients had abnormality at baseline, pro-

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Table 2. Laboratory Abnormalities of the 25 Patients with Ventilator-Associated Cytomegalovirus Pneumonia

Leukocyte count ($\text{g} \cdot \text{L}^{-1}$)	15.1 ± 6.7 (7.6–38.0)
Neutrophils (%)	83 ± 7 (68–97)
Lymphocytes (%)	9 ± 4 (2–17)
Mononucleosis picture of the peripheral blood smear	3 patients
Hemoglobin (g/dl)	9.4 ± 1.8 (7.2–13.8)
Thrombocyte count ($\text{g} \cdot \text{L}^{-1}$)	220 ± 144 (30–552)
PaO_2 (mmHg)	72 ± 16
$\text{PaO}_2/\text{FiO}_2$ (mmHg)	115 ± 35
PaCO_2 (mmHg)	47 ± 12
ASAT	31 ± 24 (9–89)
> 2 \times normal	4 patients
ALAT	48 ± 54 (7–194)
> 2 \times normal	5 patients
Serum bilirubin ($\mu\text{mol/l}$)	54 ± 73 (5–339)
> 1.5 \times normal	10 patients
Serum creatinine ($\mu\text{mol/l}$)	121 ± 91 (41–483)
> 120 $\mu\text{mol/l}$	10 patients

Values are mean \pm SD (range).

ASAT = aspartate aminotransferase; ALAT = alanine aminotransferase.

thought to infect 70% of adults but generally remains asymptomatic and silent, although it may be reactivated and produce lesions at any time during the life of the host. There is also a growing body of evidence for exogenous transmission of CMV even in seropositive patients, with the risk of acquiring viral infection linked to the number of transfused units.²¹ Although a lack of evidence for nosocomial transmission of CMV has been demonstrated,²² Faix²³ showed that contaminated objects may retain live virus and therefore potential infectious ability for several hours after contamination. This possibility stresses the need for hand washing before and after contact with CMV-infected subjects or environmental objects possibly contaminated by infected secretions.

Clinical and Radiologic Aspects of Ventilator-associated Cytomegalovirus Pneumonia

We found that clinical features were not useful in differentiating CMV from bacterial infection. It should be noted, however, that the cases of CMV pneumonia were diagnosed after a longer period of mechanical ventilation (median, 18 days) than cases of bacterial VAP as reported in the literature.²⁴ Chest radiograph played only a small role in the diagnosis of CMV pneumonia. All ICU patients had some type of radiographic abnormality at baseline, probably reflecting interstitial

edema, atelectasis, scarring, or other postoperative changes. Episodes of CMV pneumonia were superimposed upon baseline radiographic abnormalities, making it difficult to identify subtle changes. However, we found that radiographic infiltrates were generally bilateral (median Weinberg's score, 9) associating interstitial and alveolar infiltrates.

Nonhistologic Diagnostic Procedures in the Diagnosis of Ventilator-associated Cytomegalovirus Pneumonia

As clinical and radiologic signs lack specificity and even sensitivity, it would seem necessary to use virologic methods to diagnose CMV pneumonia. Rapid diagnostic techniques (*e.g.*, centrifugation cultures, which are read within 16–48 h) could be performed on BAL, blood, and urine products. These techniques are more useful in the treatment of ICU patients than conventional cultures, which require 1–4 weeks to diagnose CMV. The sensitivity of these techniques varies in the literature and has not been evaluated in mechanically ventilated patients. Thus, comparing a shell vial culture technique with conventional viral culture of lung tissue in marrow transplant patients, Crawford *et al.*²⁵ found a sensitivity of 96% with this rapid culture technique. Other authors have found that between 60% and 70% of the specimens positive by shell vial assay yield CMV by conventional culture method.^{26–28} It has even been reported that shell vial assay could be negative in 59% of the blood specimens that are positive with conventional tube cultures.²⁸ Our results showed that sensitivity of shell vial assay was low, 53% for BAL culture and 20% or less for blood and urine cultures. Conversely, and as published previously,²⁵ we found a good specificity for the shell vial assay (92%). Some recent diagnostic procedures are available for clinicians. For example, Erice *et al.*²⁹ reported that CMV antigenemia assay was significantly more sensitive than shell vial cultures of CMV in the polymorphonuclear leukocyte fraction of blood leukocytes. The CMV antigenemia assay is relatively simple to perform and may be completed in 5–6 h.

Table 3. Evolution of the 25 Patients with Ventilator-associated Cytomegalovirus Pneumonia

Ganciclovir treatment	8 patients (mortality 50%)
Duration of ganciclovir therapy (8 patients) (days)	18 ± 8 (6–31)
Duration of mechanical ventilation (days)	31 ± 22 (7–90)
Duration of hospitalization (days)	45 ± 34 (15–150)

One of the most important features of the antigenemia assay is that it can be quantified and that high levels of antigenemia appear to correlate with CMV disease.³⁰ Polymerase chain reaction has found an ever-increasing number of clinical applications, including CMV diagnosis. The method has some major pitfalls. Owing to its high sensitivity, even a small trace of contaminating DNA can cause false-positive results. False-negative results may be caused by the genetic variability of clinical strains of CMV, because altered nucleotide sequence may prevent annealing of the primers. Development of a rapid and sensitive double polymerase chain reaction to detect conserved sequences from the immediate early gene of human CMV could help to differentiate latency from active infection.³¹ We are currently evaluating antigenemia and double polymerase chain reaction for the diagnosis of CMV pneumonia in ICU patients.

Is CMV infection of the lung a clinically significant process justifying specific antiviral therapy? If so, are conventional pulmonary diagnostic techniques sufficiently sensitive and do they provide for early detection of CMV pneumonia to initiate an optimal treatment program? Discrepancies between our results and those of other investigators concerning the existence of CMV as a causative agent of VAP indicate that additional studies are needed to determine the incidence and mortality of CMV pneumonia in patients whose lungs are mechanically ventilated. These studies will no doubt use shell vial culture techniques, antigenemia, and polymerase chain reaction assay. The main problem is that none of these techniques has been validated in the diagnosis of ventilator-associated CMV pneumonia. Nevertheless, these new techniques may not necessarily increase specificity in diagnosing CMV pneumonia. Under these circumstances, precise diagnosis of CMV pneumonia continues to rely on documenting CMV inclusions on tissue specimens obtained by open-lung biopsy or transbronchial lung biopsy and improved methods for diagnosing CMV pneumonia are required.

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