Incidence and Morbidity of Cytomegaloviral Infection in Patients with Mediastinitis following Cardiac Surgery*

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To determine the incidence and morbidity of infection with CMV associated with mediastinitis after conventional cardiac surgery, 115 consecutive adult patients with mediastinitis were evaluated with viral cultures of blood and urine. Shedding of CMV was seen in 29 patients (25 percent) within a mean period of 37 ± 22 days after cardiopulmonary bypass. Viremia was documented in 79 percent (23) of these 29 patients. Acute renal failure and enzymatic abnormalities (AST and LDH) were significantly more common in patients with virologically proven infection with CMV (p < 0.05). In patients who survived the initial period of bacterial infection, major differences in their clinical course were observed according to their virologic status. After the 15th day of hospitalization following the débridement, the persistence of local infection was more frequent (p < 0.05) and the mortality was higher (p < 0.01) in CMV-infected patients. Moreover, the mean duration of hospitalization in the ICU for survivors was 69 ± 36 days in viral shedders, compared with 48 ± 27 days in nonshedders (p < 0.05). Infection with CMV in mediastinitis occurs frequently and is associated with persistence of local infection, prolonged hospitalization, and increased late mortality. (Chest 1990; 97:18-22)

Infection with CMV following cardiac surgery was first recognized as a syndrome resembling infectious mononucleosis, and in most cases, documented infection with CMV in nonimmunosuppressed adults produces little, if any, disease; however, concomitant viral infection may increase susceptibility to and severity of sepsis in patients with bacterial infection. Immunologic disturbances with CMV infection have been demonstrated in vitro, in animals, and in humans.

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In particular, natural killer cell activity, T cell proliferation to mitogen and antigen, and polymorphonuclear mobilization and function have been found to be impaired by infection with CMV. Once colonized or infected by bacteria at the time of surgery, the CMV-infected host may be unable to eradicate the infecting organism. Such examples are seen in renal-transplant recipients, where concomitant bacteremia and cytomegaloviremia result in higher morbidity and mortality, and in cardiac-transplant recipients, where bacterial or fungal pulmonary superinfections occur.

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Materials and Methods

Patients

From January 1981 to June 1986, some 136 consecutive adult patients were admitted to the ICU of Bichat Hospital, Paris, referred from seven Parisian surgical departments because of mediastinitis following cardiac surgery. Patients were included in the study when viral cultures could be performed within ten days after surgical débridement. Ten patients died before the cultures could be performed, and 11 others were excluded because of toxic or contaminated cultures. The group studied was therefore 115 patients whose clinical characteristics (mean ± SD) were as follows: mean age, 57 ± 13 years; sex ratio, 16 percent female (19/115); and type of initial surgery: coronary artery bypass graft (n = 34); valve replacement (n = 62); combined procedure (n = 6); or miscellaneous (n = 13) (Table 1).

Record of Illness

The following data were recorded to determine the possible influence of CMV infection on morbidity: first-day APACHE II score; maximal abnormalities during hospitalization for hemoglobin (lower level); WBC differential count; presence of atypical lymphocytosis; serum levels of creatinine, bilirubin, AST, ALT, and LDH; maximal abnormalities on the chest roentgenogram using a
radiologic score modified from Weinberg, duration of hospitalization; and final clinical outcome.

Viral Cultures

Samples of blood and urine were obtained within ten days (mean, 4.5 ± 3 days) after diagnosis of mediastinitis. The mean interval between the initial surgical procedure and the first viral culture was 21 ± 11 days, and additional cultures were performed during the course of hospitalization every three weeks, leading to a total of 228 samplings for the 115 patients. Fresh specimens of blood and urine were inoculated onto cultures of human fibroblasts (MRC5 cells; Merieux Lab) and evaluated weekly for six weeks for cytopathologic effect typical of CMV infection.

Serology

IgG antibody titers to CMV were determined by a microtiter complement-fixation test (reference antigen: Behring Lab), with titers less than 1/8 considered negative. In 78 of the 115 patients, CMV-IgG titers could be determined within 30 days following ECC; thus, the preoperative status could be approximated.

Statistical Analysis

All comparisons were done by χ² test with Yates' correction.

RESULTS

Incidence of CMV Excretion

Clinical characteristics of the 115 patients are shown in Table I. Viral shedding was found in 29 (25 percent) of 115 patients, with CMV isolated from the blood in 20, from urine in six, and from both sites in three patients. The age, type of surgery, delay between ECC and first viral cultures, and serologic status were not different between VE+ and VE- patients. A significant difference was observed in the sex ratio, with 31 percent females (9/29) in VE+ patients vs 10 percent (9/86) in VE- patients (p<0.02).

Among the 78 patients who had CMV-IgG determination within 30 days following ECC, 22 (28 percent) had IgG titer greater than 1/8, similar in VE+ patients (8/22; 36 percent) and VE- patients (14/56; 25 percent).

Figure 1 shows the three-month distribution of mediastinitis during the study. We observed no seasonal variations in the rate of CMV excretion, but since January 1985, there was a trend towards a higher rate of infection. The mean delay between the ECC and the first positive viral culture in the group of VE+ patients was 37 ± 22 days (range, 9 to 96 days), which

Table I—Characteristics of Patients at Entry into Study*

<table>
<thead>
<tr>
<th>Data</th>
<th>VE+</th>
<th>VE-</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>29</td>
<td>86</td>
<td>115</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>59 ± 29</td>
<td>56 ± 14</td>
<td>57 ± 13</td>
</tr>
<tr>
<td>First-day APACHE II score*</td>
<td>15 ± 8</td>
<td>14.3 ± 7</td>
<td>14.6 ± 7.3</td>
</tr>
<tr>
<td>Culture day after surgery</td>
<td>22 ± 12</td>
<td>21 ± 11</td>
<td>21 ± 11</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG†</td>
<td>9</td>
<td>25</td>
<td>34</td>
</tr>
<tr>
<td>Valve replacement</td>
<td>17</td>
<td>45</td>
<td>62</td>
</tr>
<tr>
<td>CABG and valve replacement†</td>
<td>1</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>2</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Sex ratio (F/M)</td>
<td>98/20</td>
<td>97/77</td>
<td>19/97</td>
</tr>
<tr>
<td>Seropositive patients (IgG)</td>
<td>8/22</td>
<td>14/56</td>
<td>22/78</td>
</tr>
<tr>
<td>titer &gt;1/8 within 30 days after ECC</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*APACHE II, Acute physiology and chronic health evaluation (APACHE) II system for classifying severity of disease. 14
†CABG, Coronary artery bypass graft.
§p<0.02 vs VE- patients.
Table 2—Laboratory Abnormalities and Systemic Manifestations in Patients with Mediastinitis*

<table>
<thead>
<tr>
<th>Data</th>
<th>VE+</th>
<th>VE-</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>29</td>
<td>86</td>
</tr>
<tr>
<td>Hematologic features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical lymphocytosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>16 (55)%</td>
<td>26 (30)%</td>
</tr>
<tr>
<td>&gt;2000/cu mm</td>
<td>9 (31)%</td>
<td>6 (7)%</td>
</tr>
<tr>
<td>Erythrocyte count × 10^12/mm</td>
<td>3.34±0.41</td>
<td>3.36±0.51</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>9.95±1.3</td>
<td>10±1.5</td>
</tr>
<tr>
<td>WBC count × 10^3/cu mm</td>
<td>12.78±5.800</td>
<td>12.86±6.500</td>
</tr>
<tr>
<td>Lymphocyte count × 10^3/cu mm</td>
<td>3.06±0.207</td>
<td>2.19±0.000</td>
</tr>
<tr>
<td>Enzymatic abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>percent of patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak AST elevated</td>
<td>83%</td>
<td>47%</td>
</tr>
<tr>
<td>&gt;2 × normal</td>
<td>61%</td>
<td>24%</td>
</tr>
<tr>
<td>Peak ALT elevated</td>
<td>52%</td>
<td>31%</td>
</tr>
<tr>
<td>&gt;2 × normal</td>
<td>38%</td>
<td>31%</td>
</tr>
<tr>
<td>Peak LDH elevated</td>
<td>97%</td>
<td>81%</td>
</tr>
<tr>
<td>&gt;2 × normal</td>
<td>46%</td>
<td>23%</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Serum bilirubin &gt;1.5%</td>
<td>55%</td>
</tr>
<tr>
<td>× normal</td>
<td>Serum creatinine &gt;4%</td>
<td>55%</td>
</tr>
<tr>
<td>Pulmonary impairment</td>
<td>Radiologic scorea &gt;4/12</td>
<td>62%</td>
</tr>
</tbody>
</table>

*pTable values are numbers of patients unless otherwise stated; numbers within parentheses are percents.
†p<0.05 vs VE − patients.
‡p<0.01 vs VE − patients.

was similar to the mean delay observed between ECC and the last negative culture in VE − patients (39±25 days).

**Morbidity**

Laboratory abnormalities are shown in Table 2. The incidence of atypical lymphocytosis was significantly increased in VE + patients, compared with VE − patients (55 percent [16/29] vs 30 percent [26/86], respectively; p<0.05), especially when considering a threshold above 2000/cu mm (31 percent [9/29] vs 7 percent [6/86], respectively; p<0.01). Frank mononucleosis-like reaction was observed in four of six patients with isolated viruria. Elevations in AST greater than one times normal and in LDH greater than two times normal were significantly more frequent in VE + patients; the same trend was observed with jaundice, although it was not significant. Acute renal failure occurred in 16 (55 percent) of 29 VE + patients and in 27 (31 percent) of the 86 VE − patients (p<0.05).

Two protocols for treatment are currently used for acute mediastinitis in our unit, depending on the size and depth of débridement. The first technique consists of twice-daily dressings of the open wound, and the second is closed irrigation-lavage. In the group of patients treated with the latter method, evaluation of the local infection can be easily and objectively assessed, because failure of this method necessitates reoperation because of persistent signs of local or general sepsis. Of the 57 patients treated with closed irrigation-lavage in this study, 24 were definitively cured, and 33 required reoperation. Only three (13 percent) of 24 cured patients were viral shedders, compared to 12 (36 percent) of 33 patients who required reoperation (p<0.05). Thus, failure of local treatment with a need for reoperation occurred in 12 (80 percent) of 15 patients with virologically proven CMV infection.

The overall mortality during the study period was 41 percent (47/115): 37 percent (31/86) for VE − patients, and 55 percent (16/29) for VE + patients (NS). When considering late mortality (ie, after the 15th day of hospitalization), a significant difference was observed in regard to the virologic status: 16 (55 percent) of 29 VE + patients subsequently died vs 18 (25 percent) of 73 VE − patients (p<0.01). The mean duration of hospitalization among the 68 survivors was 20 days longer in VE + patients (69±36 days), compared to VE − patients (48±27 days) (p<0.05). In addition, 62 percent (8) of the 13 VE + survivors required more than 60 days of hospitalization vs 27 percent (15) of the 55 VE − survivors (p<0.05). A similar trend concerning the late mortality and the duration of hospitalization among survivors was noted when taking into account the modalities of the initial local treatment (open dressing or closed irrigation-lavage). Prior serologic status did not modify the morbidity observed in VE + patients.

**DISCUSSION**

As early as 1968, blood transfusions used in cardiac surgery had been shown to be associated with risk of CMV infection, as evidenced by CMV serologic response;4,14,17 however, the incidence of reported CMV infection fluctuates between 40 percent in earlier studies4,5,17 and 1.5 to 12 percent in recent reports18-21 and, when considering only viremia, between 0 and 1 percent.19,20 In our experience, such an incidence is low; during the period of October 1985 through June 1986, we studied 30 outpatients with an uneventful course six weeks after cardiac surgery, and only one of them had viremia. In organ-transplant recipients, the incidence of CMV infection varies from 50 to 80 percent when combining serologic, culture, and histopathologic findings5,23 and is about 20 percent when considering viremia following either marrow (18 percent), renal (29 percent), or cardiac (20 percent) transplantation.5,24,25 Most research on CMV infection after cardiac surgery relies on serologic analysis. In our study, the laboratory diagnosis of CMV infection...
depended on isolation of the virus. The sensitivity and precision of this approach is outstanding for viremia, but there have been conflicting reports on the reliability of CMV detection in urine. Our choice of including urine cultures was guided by two considerations: (1) previous studies demonstrated a very low (less than 1 percent) rate of viruria due to CMV in normal adults; and (2) all six viruric subjects reported ill effects (atypical lymphocytosis, four; enzymatic abnormalities, six; jaundice, four; renal failure, four; and CMV-IgM presence, two) which were similar to viremic patients. Therefore, using the criteria of viral shedding, we have shown CMV infection in 29 of 115 patients suffering mediastinitis after open-heart surgery, for an incidence of 25 percent. Viremia was documented in 79 percent (23/29) of these patients.

Although it may be thought that the frequency of CMV infection fluctuates, depending on immunologic disturbances observed in patients in the ICU, we were unable to find any published data that could substantiate such a statement. In our experience the rate of CMV shedding does not seem to be critically dependent on the severity of the patient's status; for instance, it is important to underline that the indicator of severity of disease that we used, the APACHE II score, was the same (14.6 ± 7.3) on the day of admission, whether patients subsequently proved to have CMV infection or not. Moreover, during the period of October 1985 through June 1986, only four of 36 patients who required prolonged care in our ICU (first-day APACHE II score: 16 ± 8) after cardiac surgery for reasons other than mediastinitis were viral excretors. During the same period, 11 of 35 patients with mediastinitis evidenced viral shedding. There is a growing body of evidence for exogenous transmission of CMV even in seropositive patients, with the risk for acquiring viral infection linked to the number of transfused units. It is likely that our patients had received more blood products than the average currently required for standard ECC, because the duration of surgery is longer and reexploration for hemorrhage more frequent in patients who ultimately become infected. Although this warrants further study, it is unlikely that the observed rate of viremia (20 percent) can be directly related to the number of units transfused. Unfortunately, we could not assess this point because of the number of referring surgical departments.

We were unable to evidence any correlation between viral shedding and CMV serology; this may be due to the lack of sensitivity or specificity of the complement-fixation test or to a lack of serologic response from critically ill patients. Conversely, we observed a significantly higher rate of viral infection in female patients. While it is not clear why female patients were more susceptible to CMV infection, this observation agrees with the higher rate of seroconversion to CMV reported by Wilhelm in female patients receiving blood transfusion but not undergoing cardiac surgery or kidney transplantation. We also observed a trend towards an increase of CMV infection during the year of 1985 (Fig 1), while laboratory techniques and staff were unchanged. Concomitantly, the HIV serologic status became available for blood donors and screening was made mandatory by order of the French Health Department in July 1986. We postulate that a subpopulation of hidden high-risk donors gave blood in an attempt to obtain the results of their own HIV serologic status. This point is substantiated by a recent official report where a tenfold higher proportion of HIV+ status among new donors was found, compared with regular donors during the year of 1986 (0.2 percent vs 0.02 percent, respectively).

The pathogenicity of CMV in the normal adult host is extremely variable. In our study, while anemia and leukocytosis were present in both viral and non-viral excretors, we noted a mild trend towards lymphocytosis in the former group (Table 2), without high absolute counts. This fact may be explained by the lymphopenia regularly associated with severe bacterial sepsis. A definite mononucleosis-like reaction on blood smears was seen for one third of the VE+ patients, consistent with earlier studies. Jaundice was not more common in VE+ patients, and although over 80 percent of the patients with CMV infection had elevated enzymes, severe cytolytic was uncommon.

By contrast, a rather unexpected finding was the frequent association of acute renal failure with CMV infection. Glomerular and interstitial injuries, which have been described in CMV infection, may contribute to other well-known mechanisms such as hemodynamic disturbances, sepsis, and toxicity of antimicrobial agents, to produce the observed high incidence of acute renal insufficiency.

A noteworthy finding in our study was the impact of CMV excretion on the severity of bacterial infection, especially after the 15th day of sepsis (36 ± 11 days after cardiac surgery). The higher late mortality and the longer duration of hospitalization seen among VE+ survivors support this finding. We likewise observed that failure of initial treatment was significantly more frequent for viral excretors. Although it could be argued that among the patients with mediastinitis, those with higher morbidity and more prolonged hospitalization would have been recognized more frequently as VE+ because of more frequent cultures, certain findings suggest that this was not a bias. First, the mean delay observed between ECC and the first positive culture in VE+ patients was similar to the mean delay observed between ECC and the last negative culture in VE− patients; and, secondly, the mean number of viral cultures performed
until the first positive culture in VE+ patients was 1.72 ± 0.70 cultures per patient vs a total number of 1.81 ± 0.74 cultures per patient in the VE− group (NS).

In conclusion, we believe that CMV infection enhances the morbidity of the infectious process in the setting of severe mediatinitis following cardiac surgery in adult patients. The therapeutic significance of this finding should be evaluated by a placebo-controlled trial of antiviral agents, provided nontoxic drugs become available.

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