The Importance of Cytomegalovirus in Heart-Lung Transplant Recipients

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The first 33 heart-lung transplant recipients in our series were studied for evidence of CMV infection. CMV infection was diagnosed by a change in the serologic status, viral culture, or histology of lung tissue. Of 18 patients who were preoperatively negative for CMV antibody, eight received organs from CMV antibody-positive donors. Five developed pneumonia (fatal in three); one survived primary CMV of the GI tract. Those who recovered from CMV pneumonia received IV ganciclovir with CMV hyperimmune globulin given prophylactically from the time of transplantation. Only three of ten antibody-negative patients receiving organs from antibody-negative donors developed primary CMV, characterized by only fever in two but associated with rejection, and repeated infection was fatal in a third. CMV reactivation/reinfection occurred in seven of 15 (47 percent) without clinical disease in all but one case. Following heart-lung transplantation, CMV is the cause of considerable mortality and morbidity. We recommend that CMV antibody-negative recipients should receive organs only from antibody-negative donors. If a donor/recipient mismatch occurs, hyperimmune globulin and ganciclovir may improve survival. (Chest 1989; 95:627-31)

Cytomegalovirus (CMV) infections occur throughout the world.1 Epidemiologic studies have shown that in Europe and North America 60 to 70 percent of adults possess antibodies against CMV. In immunocompetent persons CMV infections are usually asymptomatic but become clinically important in the very young and the elderly.2-4 Also, serious infections occur in newborns who acquire the infection congenitally, in patients with malignant disease, and following massive transfusions of blood.2-4 In the immunologically compromised patient with human immunodeficiency virus (HIV) infection5 or the immunosuppressed patient following transplantation, CMV infections are often severe or fatal.6-11

In bone marrow12 and organ transplantation6-11 there is now good evidence that CMV disease may be transmitted with the donor organs. We report the incidence of CMV disease in a series of heart-lung transplant recipients. The importance of organ transmitted disease is discussed and the results of a CMV matching policy presented. Recommendations are made for prophylaxis and treatment of CMV disease.

MATERIAL AND METHODS

Patients

All patients who received a heart-lung transplant between April 1984 and November 1987 were included in this study. Procedures for donor and recipient selection, organ preservation, and operative techniques have been described previously.10-12 Immunosuppressive therapy is summarized in Table 1. The preoperative CMV antibody status of the recipients was established by determining the CMV complement fixation antibody titer. A latex agglutination test* (Becton Dickinson) for detecting CMV antibody was also performed on serum samples from recipients and donors. In the first 17 transplants, CMV status of the donor was not used as a criterion for recipient selection.

Diagnostic Criteria

The CMV complement fixation antibody titers17 were measured weekly during the initial hospital admission and at each subsequent outpatient attendance every one to three months. A diagnosis of primary CMV infection was made in patients whose serum had a preoperative CMV antibody titer of <8 with a subsequent >fourfold rise in CMV antibody titer and CMV-specific IgM.18 The diagnosis was confirmed by viral culture from the urine or, in the case of CMV pneumonia, by the demonstration of typical “owl eye” inclusion bodies on transbronchial biopsy taken through a fiberoptic

### Table 1

<table>
<thead>
<tr>
<th>Drug/Dosage</th>
<th>Patient No.</th>
<th>Patient No.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-5</td>
<td>6-33</td>
</tr>
<tr>
<td>Period</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perioperative</td>
<td>Cyclosporine</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td></td>
<td>4-6 mg/kg</td>
<td>4-6 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Methylprednisolone</td>
<td>Methylprednisolone</td>
</tr>
<tr>
<td></td>
<td>1g + 125 mg x 3</td>
<td>1g + 125 mg x 3</td>
</tr>
<tr>
<td></td>
<td>Equine ATG* x 3</td>
<td>Equine ATG* x 3</td>
</tr>
<tr>
<td></td>
<td>days</td>
<td>days</td>
</tr>
<tr>
<td>Maintenance</td>
<td>Cyclosporine</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td></td>
<td>6-10 mg/kg/day</td>
<td>6-10 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>Prednisolone</td>
<td>Prednisolone</td>
</tr>
<tr>
<td></td>
<td>0.2 mg/kg/day</td>
<td>0.2 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>Azathioprine</td>
<td>Azathioprine</td>
</tr>
<tr>
<td></td>
<td>3 mg/kg</td>
<td>Adjusted to keep</td>
</tr>
<tr>
<td></td>
<td>WBC &gt;5,000/mm$^3$</td>
<td>WBC &gt;5,000/mm$^3$</td>
</tr>
</tbody>
</table>

*Antithymocyte globulin.
Cytomegalovirus
Mismatch
No
Pulmonary
Yes
GI
No
Yes
Yes
1
1
1
GI
Site
18
Pulmonary
None
Yes
Pulmonary
Yes
Yes
1
Pulmonary

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Table 2—Treatment of Primary CMV Disease in Heart-Lung Transplant Recipients

<table>
<thead>
<tr>
<th>Disease</th>
<th>Mismatch</th>
<th>Site</th>
<th>Drug</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 CMV</td>
<td>Yes</td>
<td>GI tract*</td>
<td>Acyclovir†</td>
<td>Survived</td>
</tr>
<tr>
<td>1 CMV</td>
<td>Yes</td>
<td>Pulmonary</td>
<td>Acyclovir†</td>
<td>Died</td>
</tr>
<tr>
<td>1 CMV</td>
<td>Yes</td>
<td>Pulmonary</td>
<td>Acyclovir†</td>
<td>Died</td>
</tr>
<tr>
<td>1 CMV</td>
<td>Yes</td>
<td>Pulmonary</td>
<td>Ganciclovir</td>
<td></td>
</tr>
<tr>
<td>1 CMV</td>
<td>Yes</td>
<td>Pulmonary</td>
<td>Hyperimmune Globulin¶</td>
<td>Survived</td>
</tr>
<tr>
<td>1 CMV</td>
<td>Yes</td>
<td>Pulmonary</td>
<td>Ganciclovir</td>
<td></td>
</tr>
<tr>
<td>1 CMV</td>
<td>No</td>
<td>Pulmonary</td>
<td>Ganciclovir</td>
<td></td>
</tr>
<tr>
<td>1 CMV</td>
<td>No</td>
<td>GI tract*</td>
<td>None</td>
<td>Survived</td>
</tr>
</tbody>
</table>

*Diagnosed by gastric biopsy:
†Acyclovir 400-800 mg/day.
‡CMV Globulin (Edinburgh Blood Transfusion Service).
§Phosphonoformate (Foscarnet).
¶Ganciclovir (Syntex), 2.5 mg/kg x 3 daily for 2 wks.
††Hyperimmune globulin (Biotest) - 1 mg/kg/wk.
#Herpes simplex virus.

bronchoscope or on histology of tissue obtained at autopsy.

CMV pneumonitis was diagnosed when a pulmonary infiltrate
was seen on a chest roentgenogram with clinical evidence of
pulmonary disease, in the absence of the typical appearances
of rejection on the lung biopsy* or other pathogens in the tissue or on
culture. Reactivation of or reinfection with CMV was diagnosed by
demonstration of >fourfold rise in CMV antibody titer between
the preoperative and maximum postoperative titer.

Gastrointestinal CMV was confirmed in one patient by demonstration
of typical CMV inclusions in gastric biopsy specimens
obtained by endoscopy.

Treatment

The treatment given to all patients with CMV disease is included
in Table 2. In the first three patients with CMV pneumonitis
acyclovir alone or in combination with CMV hyperimmune globulin
(Edinburgh Blood Transfusion Service) or phosphonoformate (Fosca-
rnet, Astra Laboratories) was used. The last three patients with
CMV pneumonitis received treatment with ganciclovir (Syntex Pharma-
cuticals) combined with hyperimmune globulin (Biotest Pharma) given prophylactically from the time of transplantation.

RESULTS

In the period studied 33 patients received heart-
lung transplantation. Thirty-two patients (97 percent)
survived more than one month after surgery. The one-
year actuarial survival was 78 percent. All episodes of
primary CMV disease occurred between three and
five weeks after surgery (mean + SD, 3.7 + 1.5 weeks)
with reactivation/reinfection occurring between four
and 12 weeks (mean + SD, 6.2 + 3.0 weeks).

CMV Antibody-negative Recipients

Eighteen patients (aged 26 + 10.2 years) were CMV
antibody negative prior to transplantation (Table 3). 
Primary CMV has occurred in eight (44 percent) of
these patients (Table 2). Eight CMV antibody-negative
recipients received organs from CMV antibody-positive
donors; six (75 percent) developed a primary CMV
infection. In five recipients pneumonitis was confirmed
and was the cause of death in three. Treatment
in the fatal cases was acyclovir alone or combined
with phosphonoformate (Foscarnet) or ganciclovir. Two
patients survived primary CMV pneumonitis; both re-
ceived ganciclovir and hyperimmune globulin (Biotest)
given prophylactically from the time of transplantation.

Table 3—CMV Status and Outcome Following Heart-Lung
Transplantation

<table>
<thead>
<tr>
<th>Feature</th>
<th>CMV Antibody-negative Recipients</th>
<th>CMV Antibody-positive Recipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Alive</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Empyema/Pneumonia (CMV inclusions at autopsy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obliterative bronchiolitis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Rejection, CMV, HSV*</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Tracheal dehiscence</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

*Herpes simplex virus.

Cytomegalovirus and Heart-Lung Transplant Recipients (Hutter et al)
optic transbronchial biopsy. In one patient GI CMV was confirmed by endoscopic gastric biopsy. She was treated successfully with acyclovir and CMV hyperimmune globulin (Edinburgh Blood Transfusion Service). Of the three CMV antibody-negative patients who received organs from CMV antibody-negative donors and developed primary CMV disease, one developed nausea and vomiting with abdominal pain. This was associated with a rise in CMV titer from 8 to 512. No specific treatment was given. In a second patient, CMV pneumonitis alternated with episodes of lung rejection and disseminated herpes simplex virus infection. Despite treatment in sequence with ganciclovir and acyclovir, the patient died on the 135th postoperative day. A third patient showed a rise in CMV antibody titer from 8 to 2,048 without symptoms of illness.

**CMV Antibody-positive Recipients**

Fifteen recipients (aged 34 + 7.5 years) were CMV antibody positive prior to transplantation. Reactivation of or reinfection with CMV was noted in seven (47 percent) of patients. This was symptomatic in only one patient, who had a mild pyrexia. Another patient died on day 29 following staphylococcal empyema and septicemia. CMV inclusion bodies were found on histology of lung tissue obtained at autopsy.

**Correlation of Outcome with Preoperative CMV Status** (Table 3)

Twelve of 18 (67 percent) patients in the CMV antibody-negative group are surviving. There were three deaths due to CMV pneumonitis, two due to obliterative bronchiolitis, and one from overwhelming herpes simplex virus infection with CMV pneumonitis. Eleven of 15 (73 percent) patients in the CMV antibody-positive group are surviving. There was only one death in which CMV could have contributed. This patient died from a staphylococcal empyema and septicemia, but CMV inclusions were found at autopsy. The other fatalities were due to obliterative bronchiolitis, tracheal dehiscence, and cerebral infarction.

**Influence of CMV Matching Policy** (Table 4)

Before donor-recipient CMV matching was established, seven of ten antibody-negative recipients received organs from CMV antibody-positive donors, and three died from CMV pneumonitis. A further two patients recovered following severe CMV disease (Table 3).

Since the matching policy has been established, only one of seven antibody-negative recipients has received organs from an initially incorrectly classified CMV antibody-positive donor due to a false negative latex agglutination test. This patient was given hyperimmune globulin prophylactically and has remained CMV antibody negative.

**DISCUSSION**

CMV has been a major cause of morbidity and mortality after bone marrow and organ transplantation. We have previously reported the importance of donor-transmitted disease in heart transplant recipients and in our initial experience with heart-lung transplant recipients. Recently, a study on renal transplant recipients has shown that cadaveric renal grafts can transfer an identifiable strain of CMV virus to the recipient. Among 36 pairs of kidney transplant recipients CMV viruria or viremia occurred in both members of four pairs of recipients. Restricted-enzyme analysis of viral DNA revealed that both members shed the same strain of CMV, providing strong evidence that the virus can indeed be transmitted with the donor organs.

Of particular concern in heart-lung transplant recipients is the significant mortality associated with primary CMV pneumonitis in CMV antibody-negative recipients who receive organs from CMV antibody-positive donors. A rapid test of CMV antibody status (CMV scan, Becton Dickinson) became available in 1985 and has enabled us to ensure that CMV antibody-negative recipients received organs only from CMV antibody-negative donors. Since this policy was adopted, no further deaths from organ-transmitted CMV disease have occurred. However, despite this matching policy, on one occasion a CMV antibody-negative recipient received organs from a CMV antibody-positive donor due to a false negative latex agglutination test performed at the donor hospital. The serum from the donor was later found to be antibody positive on repeated testing by the same method in Cambridge. We have found in patients being assessed for transplant that the latex agglutination test is more reliable than the complement fixation test, which can often give high titer false positive results. From our experience it seems wise that as soon as a CMV mismatch is discovered, the recipient should receive hyperimmune globulin each week. This policy has also been suggested for kidney, heart, and bone marrow transplant recipients. In a recent prospective randomized trial 59 CMV antibody-

<table>
<thead>
<tr>
<th>Feature</th>
<th>Prior to Policy (Patients 1-17)</th>
<th>After Policy (Patients 18-33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No.</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>CMV Antibody-negative recipients</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>CMV mismatch</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Symptomatic CMV disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Fatal</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 4—Influence on CMV Matching Policy**
negative patients, who received kidneys from donors who had antibody against CMV, were assigned to receive either IV CMV immune globulin or no treatment. The incidence of virologically confirmed CMV associated syndromes was reduced from 60 percent in control subjects to 21 percent in recipients of CMV immune globulin. The authors concluded that CMV immune globulin provides effective prophylaxis in renal transplant recipients at risk for primary CMV disease. Our limited experience and that of others, suggests that prophylaxis with CMV immune globulin is also effective in heart-lung transplant recipients. There is evidence that some commercial CMV hyperimmune globulin preparations are not effective in preventing CMV disease, but like others we have found that the Biotest preparation may be effective. On diagnosis of a CMV infection, particularly pneumonitis, treatment with IV ganciclovir appears effective in some situations. This drug regimen has been used successfully in two patients who developed primary organ-transmitted CMV pneumonitis. This is in contrast to three patients early in our series who did not receive this treatment regimen and died with primary CMV pneumonitis.

A variety of drugs such as vidarabine, α-interferon, and acyclovir has been used to treat CMV infections in immunocompromised patients with disappointing results. Ganciclovir 9 (1,3-Dihydroxy-2 propoxy methyl 1) guanine also known as DHPG (Syntex Pharmaceuticals) has been shown in vitro to inhibit replication of all human herpes viruses including CMV. Initial reports in patients with HIV suggested treatment with ganciclovir may result in clinical improvement, particularly in patients with extrapulmonary sites of involvement. In one report, 84 percent of patients with retinal involvement and 62 percent of those with GI involvement had clinical improvement in association with ganciclovir, but patients with CMV pneumonitis fared less well. Fifty-seven percent died before completing the two-week course of ganciclovir. It is suggested that the time required for an antiviral effect may be too long to benefit the patient with advanced CMV pneumonia. Early initial treatment was therefore recommended.

Ganciclovir has also not been shown to be effective in bone marrow transplant recipients. In one reported series, nine of ten patients died of progressive respiratory failure at a median period of 16 days from the onset of pneumonia despite cessation of viremia and viruria. However, there have been reports of successful treatment of CMV pneumonitis in renal, cardiac, and heart-lung transplant recipients with ganciclovir. It is therefore possible that the degree of immunosuppression and, in cases of organ transplantation, the organ transplanted influence the successful outcome of CMV treatment.

In our experience of CMV disease in heart-lung transplant recipients we have used a combination of hyperimmune globulin and ganciclovir successfully in the management of CMV disease. We have been impressed by the successful management of two patients who recovered after CMV pneumonitis.

In the combined series of 50 heart and five heart-lung transplant recipients reported by Dummer et al., 16 of 22 patients (73 percent) who were initially antibody negative for CMV disease became infected, and most were symptomatic, whereas 33 (100 percent) of patients who were initially antibody positive became infected, but CMV disease was symptomatic in only six (18 percent). In our series of heart-lung recipients, however, only seven of 15 (47 percent) have shown a reactivation of or reinfection with CMV, with a rise in CMV titers with symptoms in only a single case. Experience of our antibody-negative recipients is similar to that described by Dummer et al.; eight of 18 (44 percent) had primary CMV disease and six were symptomatic. The disease was fatal in three recipients. In the five heart-lung transplant recipients in the Dummer series, all developed CMV disease, and four had pneumonitis. This incidence of CMV was thought to be related to the 80 percent rate of primary infection in this group. In accordance with Dummer and others we have shown that symptomatic CMV disease is associated with primary rather than reactivated infection and occurs within the first two months following transplantation.

The spectrum of CMV infection following human heart-lung transplantation has been described in 19 survivors in the Stanford Transplant Program. It was clearly shown that CMV disease was not necessary for the development of post-transplant obliterative bronchiolitis (OB), since four patients developed OB with no evidence of CMV infections at any time and received organs of antibody-negative donors. In our series, OB has been found in only three patients. One remained CMV antibody negative throughout, one survived primary CMV assumed to be transmitted by blood products, and one had symptomatic reactivation of CMV. We believe that obliterative bronchiolitis is a consequence of inadequate treatment of rejection and is not related to CMV disease. The use of transbronchial biopsy may have enabled us to diagnose rejection earlier and more accurately, allowing more adequate treatment and thereby reducing the incidence of obliterative bronchiolitis.

We conclude that CMV is a major problem in heart-lung transplant recipients and is more severe than in heart transplant recipients. The mortality of primary pulmonary CMV transmitted with the donor organs in our series was 60 percent, although this mortality occurred prior to the introduction of our current treatment policy. However, in view of the considerable
morbidity of CMV disease and the expense of prophylaxis with hyperimmune globulin, we believe that it is preferable to avoid transplantation of organs from a CMV antibody-positive donor into an antibody-negative recipient. If a CMV mismatch does occur, hyperimmune globulin given prophylactically and ganciclovir (Syntex) given at the earliest suspicion of CMV disease may improve survival.

References