Long-term Sequelae after Recovery from Cytomegalovirus Pneumonia in Allogeneic Bone Marrow Transplant Recipients*

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The clinical course of cytomegalovirus (CMV) pneumonia in seven consecutive bone marrow transplant (BMT) recipients during a 24-month period was studied. Retrospective analysis of clinical data on the recipients with CMV pneumonia during the illness and prospective follow-up of those who recovered from the pneumonia was performed. Those who had CMV as the sole pathogen and with lymphocytosis in the BAL and the peripheral blood during the illness recovered from the pneumonia. On the contrary, those who had mixed bacterial or fungal infection with peripheral lymphopenia died. Persistent lymphocytosis in the BAL and the peripheral blood, in the absence of CMV infection, was observed in the survivors. Two subsequently developed restrictive lung disease and two had relapse of their primary malignancy. These data suggest that CMV pneumonia in BMT patients is associated with significant long-term sequelae. The phenomenon of persistent lymphocytosis in the BAL and the peripheral blood, in the absence of CMV infection, supports Grundy’s hypothesis that CMV pneumonia in BMT recipients is an immunopathologic condition.

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Cytomegalovirus (CMV) pneumonia is a major complication following allogeneic bone marrow transplantation (BMT), and it carries a mortality rate of approximately 85 percent. Treatment with an antiviral agent, such as dihydroxy-2-propoxymethyl-guanine (DHPG), has no significant impact on the outcome. However, the addition of CMV hyper-gammaglobulin (GIG) has improved the survival rate to 50 percent. This also supports the hypothesis of Grundy et al that CMV pneumonia in transplant recipients is an immunopathologic process due to the host T-cell response to the presence of viral antigens in the lung.

To our knowledge, there are no published data on the long-term outcome of BMT recipients who recovered from CMV pneumonia. In view of the hypothesis of Grundy et al, we followed the clinical course of seven consecutive BMT recipients with CMV pneumonia during a 24-month period at our center. The results indicate that there could be significant long-term complications following an apparent recovery from the pneumonia and lend support to the immunologic hypothesis.

**MATERIAL AND METHODS**

From July 1986 to June 1988, fiberoptic bronchoscopy (FOB) with bronchoalveolar lavage (BAL) was performed on 23 BMT recipients at our center. Indications for the procedure included progressive dyspnea and/or pulmonary infiltrates on chest roentgenogram (CXR) after BMT. All BALs were processed for detecting the presence of bacteria, including Legionella, mycobacterium, fungus, protozoa, and viruses. In particular, immunofluorescence studies using monoclonal antibody directed against an early nuclear antigen of CMV* in a shell vial cell culture assay was used for detecting the presence of CMV in the BAL fluid. Briefly, monolayers of fibroblast in shell vials were inoculated with the BAL fluid, the cells were then examined 16 h later with the immunofluorescent antibody directed against CMV. Diagnosis of CMV pneumonia was based on the presence of CMV in the BAL using this shell vial culture-immunofluorescent detection system. Differential cell count of the BAL fluid was also obtained.

Recipients who recovered from CMV pneumonia were followed up at regular intervals with complete blood cell count, sputum and urine cultures, CXR, and pulmonary function tests (PFT). Bronchoscopy with BAL was performed whenever indicated.

**RESULTS**

During the 24-month period, FOB with BAL was performed on 23 BMT recipients who presented with acute respiratory illness. Seven of them were diagnosed as having CMV pneumonia. The clinical characteristics of these patients are summarized in Table 1. These include their primary diagnosis, the conditioning regimens, pretransplant CMV serologic study as well as the duration after BMT when CMV pneu-
monia was diagnosed. As shown in Table 1, with the exception of case 1, all patients presented within the first six months after BMT.

The clinical presentation of CMV pneumonia as well as the outcome in each case was presented in Table 2. All patients were symptomatic on presentation; symptoms include dry cough, dyspnea, and fever. All except one patient (case 1) had bilateral infiltrates on CXR. Cytomegalovirus was the sole pathogen in four cases, and the rest had concomitant bacterial or fungal infection. The incidence of CMV pneumonia in this cohort is 31 percent, which is comparable with other studies.10

All, except one patient (case 3), were treated with DHPG and GIG. Those patients who had CMV as the sole pathogen and with peripheral lymphocytosis during the illness recovered from the pneumonia (cases 1 through 4). At the time of presentation, the mean lymphocyte counts from these four patients were 1.55 x 10^9/L, with the percentage of lymphocytes ranging from 35 percent to 73 percent (Table 2). On the contrary, fatal outcome was observed in the three patients with mixed infection and with peripheral lymphopenia. The mean lymphocyte counts from these three patients were 0.19 x 10^9/L, with the percentage of lymphocytes ranging from 2 percent to 8 percent (Table 2).

The four patients who survived the CMV pneumonia were followed up at regular intervals. At the end of the two-year period, two developed restrictive lung disease and two died of relapse from the primary hematologic disorder. Thus, in this cohort, the outcome of CMV pneumonia in BMT recipients can be divided into three subgroups: (1) survived the pneumonia but subsequently developed restrictive lung disease; (2) recovered from the pneumonia but followed with relapse of the primary malignancy; and (3) fatality.

**Restrictive Lung Disease**

In cases 1 and 2 (Table 1), both patients were seronegative to CMV pre-BMT and had acute graff-
Long-term restrictive vs-host disease (GVHD) post-BMT. Within six to nine months after recovery from the CMV pneumonia, both presented with progressive dyspnea. The BALs revealed no pathogen. The PFTs showed a restrictive defect with reduction in lung volumes and diffusing capacity (Tables 3 and 4). In case 2, diagnosis of bronchiolitis obliterans with organizing pneumonia was made on open lung biopsy specimen. The patient was treated with methylprednisolone (1 g/day) for five days and with symptomatic improvement. Methylprednisolone was then switched to oral prednisone and the dosage was gradually tapered. Repeated PFTs obtained three months later showed improvement in lung volumes as well as diffusing capacity (Table 4). In case 1, the changes in the PFT results were not as severe as in case 2. After infectious cause was ruled out by bronchoscopy, the patient's prednisone dose was increased from the maintenance dose of 7.5 mg/day to 15 mg/day. Symptomatic improvement was observed and repeated PFT three months later showed mild increase in lung volumes. However, the diffusing capacities of both patients were persistently lower than before CMV pneumonia. As shown in Table 5, data obtained from ten asymptomatic recipients from the same era showed no significant change in lung volumes, with a mild reduction in diffusion capacity (though still within the normal limits) a year after BMT. However, the diffusing capacities obtained from both patients after recovery from CMV pneumonia were lower than the mean value obtained from those who did not have CMV pneumonia a year after transplantation. Both patients are alive at the time of reporting.

Serial BALs were obtained from both patients during the follow-up period. Persistent lymphocytosis, in the absence of detectable virus by the shell vial culture technique was found in the BALs in both patients (Tables 2 and 3). The percentage of lymphocytes in the BAL fluids was significantly higher than the normal ranges at our institute. The mean profile of BAL differential obtained from seven asymptomatic BMT recipients at our institute up to 100 days after BMT is macrophages 88 percent, neutrophils 3 percent, and lymphocytes 9 percent (unpublished data). Analysis of peripheral blood also showed relative lymphocytosis during the acute illness and persisted into the recovery phase until the presentation of restrictive lung disease (Fig 1, left).

Recurrence of Primary Hematologic Malignancies

Two patients, cases 3 and 4, had relapse of the primary hematologic disease after recovery from the CMV pneumonia. In case 3, the patient was seropositive to CMV pre-BMT. During the episode of CMV pneumonia, disseminated viral replication and shedding was shown by positive shell-vial cultures from urine and oropharynx. Analysis of the peripheral blood again showed relative lymphocytosis, both during the acute illness and persisted into the recovery period without positive viral culture. In case 3, the peak percentage of lymphocyte at the time of presentation was 70 percent. The lymphocytosis persisted for three

Table 3—Serial Pulmonary Function Tests (PFT) on Case 1 and Differential Cell Count of Bronchoalveolar Lavage (BAL)*

<table>
<thead>
<tr>
<th>Time, mo</th>
<th>Pre-BMT</th>
<th>Post-BMT</th>
</tr>
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<tbody>
<tr>
<td>Post-BMT</td>
<td>30 41 42 46 49 55</td>
<td></td>
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<tr>
<td>Post-CMV</td>
<td>0  1  5  8  14</td>
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Table 4—Serial Pulmonary Function Tests (PFT) on Case 2 and Differential Cell Count of Bronchoalveolar Lavage (BAL)*

<table>
<thead>
<tr>
<th>Time, mo</th>
<th>Pre-BMT</th>
<th>Post-BMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-BMT</td>
<td>2  3  5  6  9</td>
<td></td>
</tr>
<tr>
<td>Post-CMV</td>
<td>0  1  3  4  7</td>
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Table 5—Pulmonary Function Tests in Asymptomatic BMT Recipients before and 1 Year after Transplantation*

<table>
<thead>
<tr>
<th>Time, mo</th>
<th>Pre-BMT</th>
<th>Post-BMT</th>
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<tbody>
<tr>
<td>PFT TLC, % predicted</td>
<td>105 ± 11</td>
<td>104 ± 11</td>
</tr>
<tr>
<td>RV, % predicted</td>
<td>84 ± 16</td>
<td>96 ± 23</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>107 ± 14</td>
<td>107 ± 14</td>
</tr>
<tr>
<td>Dco, % predicted</td>
<td>99 ± 20</td>
<td>78 ± 27</td>
</tr>
</tbody>
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*BMT = bone marrow transplant; CMV = cytomegalovirus; TLC = total lung capacity; RV = residual volume; FVC = forced vital capacity; Dco = diffusing capacity corrected for hemoglobin.
months and declined on relapse of the hematologic malignancy (Fig 1, upper right). The patient subsequently died of acute myelogenous leukemia (AML) after a second relapse. Similar phenomenon was observed in case 4, who was seronegative to CMV pre-BMT. Peripheral lymphocytosis was observed during CMV pneumonia and persisted prior to the relapse of acute leukemia (Fig 1, lower right).

**Patients with Mixed Infection**

The BALs obtained from cases 5, 6, and 7 during the acute illness showed evidence of mixed bacterial or fungal infection with CMV. Klebsiella and Enterobacter were identified in one case, Legionella in the second, and Aspergillus in the third case (Table 2). All were treated with DHPG and GIG, with appropriate antibiotics or antifungal agents. None survived the acute illness. Analysis of peripheral blood found profound lymphopenia in all three patients at the time of illness (0.12, 0.14, and 0.32 ×10⁹/L, respectively) (Table 2). Thus, concurrent bacterial or fungal infection in BMT recipients with CMV pneumonia and lymphopenia carried an extremely poor prognosis.

**DISCUSSION**

In the past, CMV pneumonia in BMT recipients carried a high mortality rate. Combination therapy of DHPG and GIG has improved the survival rate to 50 percent. Similar success rate was observed in our study. Grundy et al. have proposed that CMV pneumonia in BMT recipients is an immunologic disease, with the primary pathologic process being an activated host immune response to the presence of viral antigen(s) in the lung. The consequence of this activated host immune system is not known, as there are no published data on the long-term sequelae of BMT recipients who recovered from CMV pneumonia (to our knowledge). In the present study, four patients recovered from the pneumonia. Two developed restrictive lung disease within six to nine months and
two died of relapse from the primary malignant neoplasm within five months after recovery from CMV pneumonia. Thus, our results seem to suggest that there is significant morbidity and mortality associated with BMT recipients who recovered from CMV pneumonia.

During the acute illness, lymphocytosis was found in the BAL fluid obtained from both patients who subsequently developed restrictive lung disease, suggestive of an activated host immune system induced by the viral infection. More importantly, the BAL lymphocytosis persisted in both patients in the absence of positive viral culture, following recovery from CMV pneumonia. This indicates that the activated immune system might not subside with the elimination of CMV from the body. The fact that both patients developed restrictive lung disease, in the presence of the BAL lymphocytosis, within six to nine months after recovery from CMV pneumonia suggests a cause and effect relationship between the two observations. This would support the hypothesis that CMV pneumonia in BMT recipients in an immunopathologic condition, and suggests CMV pneumonia in BMT recipients can be associated with short-term mortality as well as long-term sequelae.

Two patients who survived the CMV pneumonia had recurrence of the primary malignancy. Peripheral lymphocytosis was noted in both patients during the illness and persisted into the recovery phase (Fig. 1, upper and lower right). Recently, Milburn et al, reported nonspecific polyclonal B-cell activation in BMT recipients who had CMV pneumonia. These data suggest that CMV infection results in nonspecific polyclonal activation of hematopoietic cell lines, including malignant ones, and may play a role in relapse of the primary disease in these two patients. However, it should be emphasized that this remains a hypothesis at present and more data are needed to support this postulation.

Peripheral lymphocytosis was observed in all patients who had CMV as the sole pathogen (cases 1 through 4) and recovered from the illness, whereas all three patients who had mixed infections and died of the pneumonia had substantially lower lymphocyte counts in peripheral blood. (The mean absolute lymphocyte count was $1.55 \times 10^9/L$ vs $0.19 \times 10^9/L$.) These data suggest that the immunocompetency of the host is an important factor in determining the outcome of CMV pneumonia in BMT recipients, and peripheral lymphocytosis at the time of illness may be used as a prognostic factor for recovery.

In summary, the following conclusions can be drawn from the results of this study. First, there are long-term sequelae in BMT recipients who recovered from CMV pneumonia. In our study, these patients either developed restrictive lung disease or had relapse of the primary malignancy. Second, the phenomenon of persistent lymphocytosis in the BAL and the peripheral blood, in the absence of positive viral culture, supports Grundy’s hypothesis that CMV pneumonia in BMT patients is an immunopathologic condition. Third, peripheral lymphocytosis during CMV pneumonia may be used as a prognostic factor for recovery from the illness, as recovery occurs only in patients who were able to mount the response in the peripheral blood during the illness.

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REFERENCES