is ubiquitous and has been isolated from a variety of natural substances, including farm soil, marine soil, mature, stream water, stagnant mud water, seawage, coastal tidal sands, and poultry and cattle manure worldwide. The two most common clinical conditions caused by *P. boydii* are mycetoma and respiratory tract involvement by colonization of preformed cavities. In addition to potential geographic exposure due to her rural residence, the additional impact of the patient’s augmented immunosuppression 6 to 7 months prior to her presentation may have contributed to the development of this fungal infection. Previous case reports have implicated similar mechanisms in the acquisition of infection by immunocompromised patients.

Blood culture findings positive for *P. boydii* have been reported in patients with leukemia and AIDS. This is the first reported case of *S. apiospermum* fungemia in a transplant patient resulting in positive antemortem blood culture findings. This patient demonstrated myocarditis with extension into the papillary muscles, myocardium, coronary arteries, and pericardium; however, involvement of the endocardium (valves and intracavitary endocardium) was not present. While the patient had positive blood culture findings, she had no central lines or long-term endovascular devices until those inserted for treatment at the time of her terminal hospital admission. It is important to recognize that *S. apiospermum* resembles Aspergillus clinically and histopathologically, and they cannot be differentiated except on fungal cultures. *Scedosporium* has also been recovered from > 5% of sputum cultures from patients with cystic fibrosis, making these patients both a potential reservoir for airway inoculation of posttransplant patients, and placing them at potentially greater risk of infection. *S. apiospermum* has been known to respond poorly to treatment with amphotericin B, as was noted in this case. Treatment should include surgical intervention for limited disease whenever possible, in combination with medical therapy. Rapid identification is essential because this organism is often sensitive to imidazoles (itraconazole, voriconazole10–12) but resistant to amphotericin B, the drug of choice for treatment of Aspergillus and Fusarium infections. Diagnostic confusion with Aspergillus, uncertain therapy, and duration of therapy complicate management of this rare entity.

**Conclusion**

This case report and review of literature highlights the importance of *S. apiospermum* as an important opportunistic pathogen in transplant patients, its apparent similarity to Aspergillus and Fusarium on pathologic examination, and its inherent resistance to treatment with amphotericin B, the traditional drug of choice for invasive hyalohyphomycosis. A high index of suspicion, multiple and early cultures, and availability of the newer serologic and genetic tests are essential for appropriate antifungal therapy to be instituted in this subgroup of patients. Even with early recognition of this Aspergillus-resembling pathogen and prompt initiation of appropriate antifungal therapy, a favorable clinical response in this immunosuppressed population is highly uncertain.

**References**


**Common Features in the Onset of ARDS After Administration of Granulocyte Colony-Stimulating Factor**

Hirogaki Takatsuka, MD; Yoshinobu Takenoto, MD; Ako Mori, MD; Takahiro Okamoto, MD; Akihisa Kanamara, MD, and Eizo Kakishita, MD

**Study objective:** Respiratory disturbance caused by ARDS has been reported during administration of granulocyte-colony stimulating factor. The clinical features of such respiratory distress were investigated in this study.

**Design:** Retrospective case review.
Setting: A 1,100-bed university teaching hospital.

Patients: Five patients who had dyspnea caused by ARDS develop after chemotherapy or bone marrow transplantation (BMT) at our hospital.

Interventions: None.

Measurement and results: Levels of cytokines, human leukocyte antigen (HLA) typing, and the clinical course were analyzed to clarify common features. All five patients possessed HLA-B51 or HLA-B52, and all had fever and an enhanced inflammatory response at the time of the WBC nadir. The tumor necrosis factor (TNF)-α and interleukin (IL)-8 levels increased when respiratory distress syndrome occurred.

Conclusions: If patients with HLA-B51 or HLA-B52 have infection develop at the time of WBC nadir after chemotherapy or BMT, ARDS may occur in association with elevation of TNF-α and IL-8 during WBC recovery. (CHEST 2002; 121:1716–1720)

Key words: ARDS; granulocyte colony-stimulating factor; human leukocyte antigen; interleukin-8; tumor necrosis factor-α

Abbreviations: BMT = bone marrow transplantation; CRP = C-reactive protein; FIO2 = fraction of inspired oxygen; G-CSF = granulocyte colony-stimulating factor; GVHD = graft-vs-host disease; HLA = human leukocyte antigen; IL = interleukin; rhG-CSF = recombinant human granulocyte colony-stimulating factor; TNF = tumor necrosis factor

Recombinant human granulocyte colony-stimulating factor (rhG-CSF) is used clinically to treat neutropenia caused by chemotherapy for cancer. Administration of this agent makes patients less susceptible to infection and allows chemotherapy to be administered according to schedule, leading to enhancement of the antitumor efficacy.1 It has been reported that ARDS2 can occasionally occur when anticancer agents having pulmonary toxicity, such as bleomycin, are administered with rhG-CSF.3,4 Some reports5 have also suggested the possibility that rhG-CSF itself is involved in causing pulmonary injury. We found that ARDS developed in conjunction with rapid recovery of the WBC count in five patients receiving rhG-CSF after chemotherapy or bone marrow transplantation (BMT) at our hospital. Their clinical and laboratory data were analyzed to clarify common characteristics in the present study.

MATERIALS AND METHODS

During the 4-year period between January 1996 and December 1999, 65 patients underwent allogeneic BMT and 245 patients received conventional chemotherapy at our department. All of them received treatment with granulocyte colony-stimulating factor (G-CSF). Of the 310 patients, 5 patients had ARDS develop in conjunction with rapid recovery of the WBC count. These five patients were investigated retrospectively in the present study. The Institutional Review Board approved the project and waived the need for informed consent.

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Pulmonary toxicity was diagnosed using the following criteria of the American-European Consensus Conference on ARDS: (1) acute onset, (2) arterial hypoxemia (Pao2/fraction of inspired oxygen [FIO2] ≤ 200 mm Hg), (3) bilateral infiltrates on a frontal chest radiograph, and (4) exclusion of heart failure.2 While ARDS was present, the plasma levels of tumor necrosis factor (TNF)-α and interleukin (IL)-8 were determined. In addition, the febrile period and the maximum C-reactive protein (CRP) level during the WBC nadir after chemotherapy were monitored. Furthermore, human leukocyte antigen (HLA)-A, HLA-B, HLA-DR, and HLA-DRB1 typing was done in both the recipients and the donors. Brief case reports on the five patients are presented.

Case Report 1

A 38-year-old man underwent completely HLA-matched BMT from an unrelated donor for chronic myelogenous leukemia in the first chronic phase. Both the recipient and the donor had HLA-B51 antigen. The chemotherapy regimen for conditioning was busulfan, cyclophosphamide, and total body irradiation, while cyclosporine, methotrexate, and methylprednisolone were administered for prophylaxis of graft-vs-host disease (GVHD). This patient received an infusion of 2.8 × 10^9 cells per kilogram for BMT. Beginning at day 5, lenograstim, 250 μg/d, was administered and the WBC count began to recover on day 12. On day 16, the WBC had increased to 7.9 × 10^9/L from 1.7 × 10^9/L, and the dyspnea suddenly developed. Despite oxygen administration via mask (FIO2 0.6), Pao2 failed to rise above 50 mm Hg (6.7 kPa). A chest radiograph showed bilateral diffuse frosted-glass opacities that were indicative of ARDS (chest radiograph score of Murray’s lung injury score was 2 points). His symptoms were alleviated by methylprednisolone pulse therapy for 3 days. During the aplastic phase after transplantation, fever with daily elevation of the temperature > 38.5°C occurred for 10 days and the maximum CRP level was 13.6 mg/dL. At present, the patient is well, although chronic GVHD persists.

Case Report 2

A 29-year-old woman with acute lymphoblastic leukemia underwent BMT after her third complete remission using marrow from one HLA locus-mismatched sibling. Both the recipient and the donor had HLA-B52 antigen. She received busulfan, cyclophosphamide, and total body irradiation plus antithymocyte globulin for conditioning, while cyclosporine, methotrexate, and methylprednisolone were administered for prophylaxis of GVHD. She received an infusion of 3.3 × 10^9 cells per kilogram for BMT. Beginning at day 5, lenograstim, 250 μg/d, was administered, and the WBC count began to recover on day 17. On day 18, when the WBC count had increased to 1.9 × 10^9/L, she suddenly complained of dyspnea. Despite oxygen administration via mask (FIO2 1.0), Pao2 failed to rise above 40 mm Hg (5.2 kPa). On the same day, methylprednisolone pulse therapy, 1,000 mg/d, was started and endotracheal intubation was performed for ventilation. As in case report 1, she had chest radiographic findings indicative of ARDS (chest radiograph score

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of the Murray’s lung injury score was 4 points). On the third day of treatment, her radiographic and physical findings demonstrated marked improvement. She was eventually extubated on day 25. During the aplastic phase after BMT, fever with daily temperature elevation >38.5°C occurred for 3 days and the maximum CRP was 9.6 mg/dL. She died on day 74 due to acute GVHD.

Case Report 3

A 25-year-old man with acute myelogenous leukemia received BMT from a fully HLA-matched unrelated donor after his second complete remission. Both the donor and the recipient had HLA-B52 antigen. This patient received busulfan, cyclophosphamide, and total body irradiation for preconditioning, while cyclosporine, methotrexate, and methylprednisolone were administered for GVHD prophylaxis. BMT was done by infusing 2.95 × 10^8 cells per kilogram. Beginning at day 5, lenograstim, 250 μg/d, was administered, and the WBC count began to recover on day 11. On day 12, when the count had increased to 2.6 × 10^9/L from 0.8 × 10^9/L, dyspnea occurred suddenly. Despite receiving oxygen via a mask (FiO_2, 1.0), PaO_2 did not increase above 55 mm Hg (7.4 kPa). On the same day, methylprednisolone pulse therapy, 1,000 mg/d, was started and he was intubated for ventilation. His chest radiographic findings were similar to those of case report 1, indicating a diagnosis of ARDS (chest radiograph score of the Murray’s lung injury score was 3 points). After 3 days, there was marked improvement of the radiographic and physical findings. During the aplastic phase after BMT, fever with daily temperature elevation >38.5°C occurred for 8 days and the maximum CRP was 25.0 mg/dL. His subsequent clinical course was complicated with veno-occlusive disease, and then he died on day 24.

Case Report 4

A 61-year-old woman with acute myelogenous leukemia received idarubicin hydrochloride plus cytarabine as her first remission induction therapy. After aplasia lasting for about 14 days, she received lenograstim, 300 μg/d, for 14 days. In conjunction with rapid recovery of the WBC count, she complained of dyspnea, and chest radiographs indicated a diagnosis of ARDS (chest radiograph score of the Murray’s lung injury score was 2 points). Dyspnea was alleviated by oxygen therapy coupled with methylprednisolone pulse therapy for 3 days. Fever with daily temperature elevation >38.5°C occurred for 17 days, with the maximum CRP being 23.4 mg/dL. Her HLA type was B51. Subsequently, acute myelogenous leukemia relapsed and she died.

Case Report 5

A 60-year-old man was treated with cyclophosphamide, 1,500 mg; doxorubicin hydrochloride, 80 mg; vincristine sulfate, 2.0 mg; and prednisolone, 100 mg for diffuse large B-cell non-Hodgkin’s lymphoma. At the time of the WBC nadir lasting for 5 days after this chemotherapy, he was treated with nartogras-tim, 100 μg/d. When the WBC count increased to 4.5 × 10^9/L from 0.8 × 10^9/L, dyspnea suddenly developed. Despite oxygen administration via mask (FiO_2, 0.6), PaO_2 failed to rise above 65 mm Hg (8.7 kPa) and radiographic features of ARDS were seen as in the other patients (chest radiograph score of the Murray’s lung injury score was 2 points). His symptoms were alleviated by methylprednisolone pulse therapy for 3 days. During the WBC nadir after chemotherapy, he had fever with daily temperature elevation >38.5°C for 9 days and a maximum CRP of 12.0 mg/dL. His HLA type was B51. He is alive at present, and remission has been maintained.

Results

For the five patients who had ARDS develop during administration of G-CSF, the age, sex, underlying disease, chemotherapy regimen, duration of leukopenia, duration of fever, maximum CRP, cytokine levels, and HLA type were determined. We have previously monitored TNF-α and IL-8 levels in 25 patients receiving BMT and 20 patients receiving conventional chemotherapy. All 45 patients received G-CSF. Their HLA types were neither B51 nor B52, and respiratory dysfunction did not develop. They served as historical control subjects for the present study in five patients. The levels of both TNF-α and IL-8 were normal in the 45 patients. The levels of both cytokines remained within the normal range in patients who did not have ARDS develop. In contrast, all five patients with ARDS in the present series showed significantly increases of TNF-α and IL-8. These five patients shared the following common features: (1) HLA-B51 or HLA-B52 antigen positivity, (2) elevated IL-8 and TNF-α levels at the onset of ARDS, (3) fever during the WBC nadir before recovery of the WBC count, and (4) onset of ARDS in conjunction with rapid recovery of the WBC count (Table 1).

Discussion

ARDS is defined as acute inflammation of the lung induced by biological reaction to various insults. The pathophysiology is characterized by pulmonary edema secondary to increased capillary permeability. Adhesion of neutrophils in the circulation to vascular endothelial cells and their migration and infiltration into stroma are the mechanism that plays an important role in the pathogenesis. TNF-α and IL-8 are involved in this mechanism. A direct relationship has been recognized between G-CSF and ARDS-like pulmonary injury, but the mechanism involved remains to be clarified. A relationship between G-CSF and respiratory distress was ruled out by one report because patients not receiving G-CSF also developed ARDS during rapid recovery of the WBC count. However, an association has been suggested by some reports. All of our patients received at least one of total body irradiation, cyclophosphamide, methotrexate, and busulfan, which are treatments that are known to have pulmonary toxicity, and such toxicity may have been an important factor in the pathogenesis of ARDS. In addition, because the onset of ARDS was associated with the most rapid increase of the WBC count after administration of G-CSF, it is suspected that an increase and/or activation of neutrophils by such therapy may have an etiologic role. Furthermore, elevation of CRP and fever occurred in all five patients during the period of leukopenia. This strongly suggests that inflammation related to infection is one of the risk factors for the occurrence of ARDS after chemotherapy or BMT.

Previously, we reported two patients who had ARDS develop at the time of engraftment after BMT when the WBC count was recovering rapidly. These two patients shared three common features: (1) increased TNF-α levels before preconditioning; (2) treatment with cyclo-
phosphamide, methotrexate, and busulfan, which are harmful to the lungs; and (3) elevated levels of inflammatory cytokines. Pulmonary damage caused by these factors may have been potentiated by G-CSF through elevation of the IL-8 level. Consequently, ARDS could be considered to be one manifestation of vascular endothelial injury caused by elevated levels of IL-8, as we have suggested previously. In another study, we found that the serum TNF-α level and the incidence of cytomegalovirus-related interstitial pneumonitis were significantly increased in patients with HLA-B51 or HLA-B52 antigen. This association may have arisen from the proximity of these alleles to the gene for TNF-α, which increases the possibility of linkage between them. In the present study, all five patients who had ARDS-like pulmonary injury develop during recovery of the WBC count after G-CSF administration possessed HLA-B51 or HLA-B52. In addition, fever occurred in all five patients during the period of myelosuppression, and the onset of ARDS was associated with elevation of TNF-α and IL-8. Of the 65 patients receiving BMT, 20 patients (approximately 30%) had HLA-B51 or HLA-B52 (HLA analysis was not performed in patients receiving conventional chemotherapy). As described in the studies cited above, when the patients having HLA-B51 or HLA-B52 became febrile before or after BMT, particularly during myelosuppression, and developed inflammatory reaction, the TNF-α level increased and became significantly higher than that in patients having other HLA types. Such patients were at high risk for having complications develop, including cytomegalovirus-interstitial pneumonitis. In patients having HLA types other than B51 or B52, however, the elevation of TNF-α level was not so high even if an inflammatory reaction developed, and in many cases, cytomegalovirus-interstitial pneumonitis and other complications after BMT were mild. From these results, it seems that the risk of ARDS may be increased when the WBC count rises rapidly after administration of G-CSF in patients who fulfill the following three criteria: (1) possession of HLA-B51 or HLA-B52; (2) treatment with drugs having pulmonary toxicity, such as bleomycin, cyclophosphamide, methotrexate, busulfan, and total body irradiation; and (3) infection during the period of granulocytopenia after chemotherapy. In patients having HLA-B51 or HLA-B52, TNF-α is prone to undergo stimulation because of linkage disequilibrium. When it is stimulated, the TNF-α level increases. The elevation is particularly remarkable when it is stimulated by inflammatory reaction such as infection. The remarkable elevation induces an elevation of the IL-8 level. Consequently, it is estimated that the elevation of TNF-α and IL-8 levels induce ARDS through adhesion of neutrophils to vascular endothelial cells and their migration and infiltration into stroma as described above. In conclusion, patients who fulfill the above three criteria may require more careful monitoring when the WBC count starts to recover after chemotherapy or BMT.

Table 1—Summary of the Clinical and Laboratory Data

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, yr/Sex</th>
<th>Disease</th>
<th>Stage</th>
<th>Neutropenic Period, d</th>
<th>Febrile Period, d</th>
<th>Chemotherapy</th>
<th>Maximum CRP, mg/dL (NR &lt; 5)</th>
<th>IL-8, ng/mL (NR &lt; 5)</th>
<th>TNF-α, ng/mL (NR &lt; 5)</th>
<th>IL-8, Cytokine</th>
<th>HLA Type</th>
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<tbody>
<tr>
<td>1</td>
<td>38/Male</td>
<td>CML</td>
<td>CP</td>
<td>10</td>
<td>10</td>
<td>BU/CY/TBI</td>
<td>13.6 (12)</td>
<td>147.3 (120)</td>
<td>147.3 (120)</td>
<td>13.6 (12)</td>
<td>B51</td>
</tr>
<tr>
<td>2</td>
<td>29/Female</td>
<td>ALL</td>
<td>CR3</td>
<td>17</td>
<td>3</td>
<td>BU/CY/TBI/ATG</td>
<td>9.6 (8)</td>
<td>38.3 (30)</td>
<td>38.3 (30)</td>
<td>9.6 (8)</td>
<td>B52</td>
</tr>
<tr>
<td>3</td>
<td>25/Male</td>
<td>AML</td>
<td>CR2</td>
<td>11</td>
<td>8</td>
<td>BU/CY/TBI</td>
<td>5.6 (5)</td>
<td>35.0 (25)</td>
<td>35.0 (25)</td>
<td>5.6 (5)</td>
<td>B52</td>
</tr>
<tr>
<td>4</td>
<td>61/Female</td>
<td>NHL</td>
<td>CR2</td>
<td>14</td>
<td>9</td>
<td>IDA/RV/CR/PSL</td>
<td>2.8 (2)</td>
<td>126.8 (100)</td>
<td>126.8 (100)</td>
<td>2.8 (2)</td>
<td>B51</td>
</tr>
<tr>
<td>5</td>
<td>60/Male</td>
<td>NHL</td>
<td>CP</td>
<td>5</td>
<td>9</td>
<td>CY/ADR/VCR/PSL</td>
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<td>83.1 (65)</td>
<td>83.1 (65)</td>
<td>23.4 (20)</td>
<td>B51</td>
</tr>
</tbody>
</table>

References

1 Crawford J, Ozer H, Stoller R, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia in...

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Selected Reports