Diffuse Alveolar Hemorrhage Following Allogeneic Bone Marrow Transplantation in Children*

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Background: Diffuse alveolar hemorrhage (DAH) is a frequent life-threatening complication of bone marrow transplantation (BMT) in adults. This noninfectious pulmonary disorder is rarely reported following BMT in neonates and children.

Study objectives: To review the clinical features and course of children who underwent allogeneic BMT and developed DAH in the posttransplant period.

Design: A retrospective 6-year chart review.

Setting: Pediatric ICU in a university hospital.

Patients and interventions: At total of 138 children who had undergone allogeneic BMT for nonmalignant (n=66) or malignant (n=72) diseases.

Measurements and results: Six of 138 children (4.3%) aged 2 months to 10 years (male/female ratio, 1:1) developed DAH. Each had a fulminant course with rapidly developing severe respiratory failure, mandating mechanical ventilation within 24 h following symptom onset. They were all treated with methylprednisolone, 6 mg/kg/d for 3 days. Only one child survived, and there have been no sequelae at 2 years post-BMT. Four children died of respiratory causes, and one died of multiorgan failure.

Conclusions: DAH is a potentially fatal respiratory complication that should be included early in the differential diagnosis of acute respiratory failure in children following allogeneic BMT for both malignant and nonmalignant diseases. Therapy with high doses of steroids apparently do not affect the course of the disease. (CHEST 2003; 124:660–664)

Key words: bone marrow transplantation; diffuse alveolar hemorrhage; pediatric; respiratory failure

Abbreviations: BMT = bone marrow transplantation; DAH = diffuse alveolar hemorrhage; \( F_{\text{IO}}_2 \) = fraction of inspired oxygen; GVHD = graft-vs-host disease; TBI = total body irradiation; VOD = venoocclusive disease

Diffuse alveolar hemorrhage (DAH) is a noninfectious pulmonary complication that is associated with bone marrow transplantation (BMT) and may contribute to significant morbidity and mortality in the posttransplant period.\(^1\) This disease entity was first described by Robbins et al\(^2\) in adult patients who had undergone autologous BMT. DAH is usually identified by the presence of diffuse infiltrates seen on chest radiographs, fever, and arterial hypoxemia accompanied by cough and progressive dyspnea. The etiology of DAH is still unknown, and the diagnosis is generally established through BAL by the demonstration of progressively bloodier fluid with each instilled aliquot and by negative findings on microbiological analysis of specimens. Prompt diagnosis and therapy with high-dose corticosteroids have been proposed for improving recovery,\(^3\) but mortality from DAH in the adult population is reported as being close to 80%. DAH after BMT has been only rarely reported in children.\(^4\)–\(^6\)

In this report, we describe six children and infants who developed DAH after undergoing allogeneic BMT.

Patients and Methods

We performed a retrospective case study to identify all the infants and children who developed DAH following allogeneic BMT between January 1995 and January 2001 at the Chaim
Sheba Medical Center, Tel-Hashomer, Israel, and at the Hadassah University Hospital, Jerusalem, Israel. Both facilities are regional referral centers for pediatric BMT, caring for approximately 100 new pediatric oncology patients annually.

**Diagnosis**

The diagnosis of DAH required fulfillment of the following criteria:

1. Diffuse bilateral pulmonary infiltrates seen on chest radiographs;
2. Progressively bloodier BAL fluid with each instilled aliquot of normal saline solution from at least three separate lobes and findings of hemosiderin-laden macrophages on microscopic examination of the BAL fluid;
3. Acute hypoxemic respiratory failure defined as PaO₂/fraction of inspired oxygen (FiO₂) ratio of < 150, requiring supplemental oxygen and ventilatory support;
4. No clear bacterial, viral, or fungal pathogens detected in the BAL fluid;
5. No improvement with correction of underlying coagulopathy and/or fluid overload; and
6. No evidence of cardiogenic pulmonary edema based on clinical findings, central venous pressure measurements, or cardiac echocardiography.

The onset of DAH was defined as the earliest date when pulmonary symptoms *(ie, acute or recent development of dyspnea and hemoptysis)* correlated with objective clinical findings *(ie, chest radiographs demonstrating new pulmonary infiltrates)*. Children with coagulopathies who did not respond to standard therapy, those with severe chronic liver or kidney disease, and those with bleeding pulmonary malignancies were excluded from the study.

**Microbiological Techniques**

Cytologic specimens and bacterial, viral, and fungal cultures were obtained from the BAL fluid samples. Routine Gram stains and bacterial cultures were performed as were cultures from yeast and filamentous fungi. Viral studies included analysis for cytomegalovirus, respiratory syncytial virus, and influenza A antigen.

**Pathologic Examination**

Cutaneous graft-vs-host disease (GVHD) was diagnosed according to the criteria of Lerner et al. Venocclusive disease was diagnosed clinically (from the appearance of progressive abdominal distention and jaundice) and on autopsy using the criteria of MacDonald et al.* *(ie, fibrous obliteration of small hepatic venules).*

**Statistical Analysis**

The χ² test was used for comparison of categoric variables. A p value of < 0.05 was considered to be significant. The data are presented as the mean ± SD.

**Results**

During the 6-year study period, 6 of the 138 children (4.3%) who underwent allogeneic BMT for nonmalignant disease *(n = 66)* or malignant disease *(n = 72)* developed DAH. We could find no differences between these six children and those who did not develop DAH with regard to severity of illness, age, and whether they were more or less likely to develop GVHD or venoocclusive disease (VOD). The male/female ratio among these children was 1:1, and their mean age was 45 months *(age range, 3 to 120 months)*. They presented with DAH at a mean duration of 18 ± 12 days following allogeneic BMT. Five of 66 children *(7.5%)* who had experienced a nonmalignant genetic disease for which allogeneic BMT was performed as a curative procedure developed the disease, compared to only 1 of 72 children with malignant disease *(p < 0.05).*

The clinical characteristics of the study subjects are outlined in Tables 1, 2. They were all admitted to the pediatric ICU within 24 h of symptom onset, consisting mainly of progressive dyspnea accompanied by hemoptysis. Urgent bronchoscopy was performed within a few hours from the first appearance of symptoms and revealed progressive bloody fluid with each instilled saline solution aliquot. Each patient deteriorated and became severely hypoxic within the first 24 h of DAH onset. The lowest mean PaO₂/FiO₂ ratio for the six patients was 62 ± 12 mm Hg. Mechanical ventilation was instituted using progressively higher oxygen concentrations, pressure-controlled ventilation, and positive end-expiratory pressure titrated according to saturation aiming for a value of > 90%. No special protective lung strategy was used, and the Pco₂ level was kept between 35 mm Hg and 50 mm Hg by changing the respiratory rate. Fluid and electrolyte balances were closely

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, mo/SEX</th>
<th>Diagnosis</th>
<th>Conditioning</th>
<th>Bleeding Episodes, No.</th>
<th>Outcome</th>
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<tr>
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<td>120/F</td>
<td>Fanconi anemia</td>
<td>Cy/TBI/ATG</td>
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<td>Died</td>
</tr>
<tr>
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<td>2/M</td>
<td>Osteopetrosis</td>
<td>Cy/Bu</td>
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<td>Died</td>
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<tr>
<td>3</td>
<td>4/M</td>
<td>Omenn syndrome</td>
<td>Cy/Bu</td>
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<td>Died</td>
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<td>Cy/ATG</td>
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<tr>
<td>5</td>
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<td>Acute lymphocytic leukemia</td>
<td>Cy/TBI/ATG</td>
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<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>3/F</td>
<td>Omenn syndrome</td>
<td>Cy/Bu/TBI</td>
<td>2</td>
<td>Alive, well</td>
</tr>
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</table>

*Cy = cyclophosphamide; Bu = busulfan; ATG = antithymocytic globulin; F = female; M = male.*

Table 1—Demographic Data on Children Who Underwent Allogeneic BMT and Developed DAH*
monitored, and platelet transfusions were given to correct the thrombocytopenia, which was present in all six patients. Each child was treated with high-dose methylprednisolone (6 mg/kg/d) for 3 days. Mechanical ventilation was continued for a mean duration of 10.6 days. Five of the six children (83%) died 7.8 ± 4.3 days following the initial presentation of symptoms (27 ± 6 days post-BMT) despite intensive supportive care. The cause of death was severe protracted respiratory failure for patients 2 to 5, and multiorgan failure for patient 1 (Table 1). Patient 6 was the only survivor. Cutaneous GVHD had developed in patients 1, 4, and 6, and VOD disease had developed in patients 1, 2, 3, and 6.

**Discussion**

Aggressive chemotherapy combined with radiation therapy followed by autologous or allogeneic BMT are therapeutic procedures for both malignant and nonmalignant diseases, albeit at the cost of increased complication rates during the peritransplant period. DAH, a well-documented life-threatening noninfectious pulmonary complication, is reported to occur in as many as 1 to 10% of the adult population undergoing autologous BMT. In contrast, the appearance of this disease entity in children rarely was reported and has been published mainly as case reports among young adolescents but not in infants. The only pediatric series was reported recently by Heggen et al. In their retrospective analysis, 7 of 138 patients (5.1%; mean age, 11 years) developed DAH after undergoing allogeneic BMT with a reported mortality rate of 43% (3 of 7 patients). The present study documents the appearance of DAH in as many as 4.3% of the children and neonates following allogeneic BMT for nonmalignant and malignant disorders. The high mortality rate in our patients (83%) compared to that reported by Heggen et al can be explained by the younger age of patients in our case series. Moreover, children who underwent BMT as a curative procedure for inherited genetic conditions had an even higher complication rate (5 of 66 patients; 7.5%). These findings suggest that DAH in children who undergo BMT for nonmalignant indications may have a higher risk for DHA than those children who receive BMT for the treatment of a malignancy.

Three of the children who developed DAH received either total body irradiation (TBI) or busulfan therapy as a preparative regimen. Although both are known to be potentially toxic to the lungs, only TBI has been reported as a potential risk factor for the development of DAH, whereas the inclusion of busulfan in the preparative regimen was not associated with a similar increased risk.

We could find no published data on the risk factors for DAH in children, and we were not able to discern any when we studied the 138 charts that comprised the database of the current study. The reported risk factors for the development of the disease entity in adult patients include the following: age > 40 years; previous chemotherapy for solid tumors; fever; severe mucositis; and early WBC recovery. Fever and early WBC recovery also were found to be associated with the development of DAH among our pediatric cohort to a similar extent as that reported by Heggen et al. One theory for the pathogenesis of DAH supports the role of acute GVHD in causing the DAH. According to this hypothesis, pulmonary hemorrhage results from a disruption of the alveolar capillaries, allowing fresh blood to fill the alveolar space. GVHD and VOD were more common among our patients than previously reported for an adult population that developed DAH following BMT (ie, 20%). This is in contrast to the study by Heggen et al, in which GVHD or VOD were not mentioned among children who had DAH, or to the report by Bojko et al, stating that GVHD and VOD are not risk factors for DAH in children.

As has been previously reported in adults under-

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**Table 2—Data on Clinical Course of Children Who Developed DAH***

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time, d</th>
<th>PaO&lt;sub&gt;2&lt;/sub&gt;/FIO&lt;sub&gt;2&lt;/sub&gt;, mm Hg</th>
<th>WBC, 10&lt;sup&gt;9&lt;/sup&gt; cells/L</th>
<th>Platelets, 10&lt;sup&gt;9&lt;/sup&gt; cells/L</th>
<th>Other Organ Involvement</th>
<th>MV, d</th>
<th>Cause of Death</th>
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<tbody>
<tr>
<td>1</td>
<td>16</td>
<td>50</td>
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<td>50</td>
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<td>MOF</td>
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<tr>
<td>2</td>
<td>28</td>
<td>60</td>
<td>1.1</td>
<td>50</td>
<td>VOD</td>
<td>7</td>
<td>RF</td>
</tr>
<tr>
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<td>1</td>
<td>80</td>
<td>1.6</td>
<td>60</td>
<td>VOD</td>
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<td>RF</td>
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<tr>
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<td>75</td>
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<td>48</td>
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<td>RF</td>
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<tr>
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<td>2.5</td>
<td>18</td>
<td></td>
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<td>RF</td>
</tr>
<tr>
<td>6</td>
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<td>60</td>
<td>2.0</td>
<td>24</td>
<td>GVHD-I, VOD</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>

*Time = duration between allogenic BMT and onset of DAH; ARF = acute renal failure; MOF = multiorgan failure; RF = respiratory failure; MV = mechanical ventilation; I = grade I; IV = grade IV. Data on PaO<sub>2</sub>/FIO<sub>2</sub>, WBC count, and platelet count refer to worst values in the first 24 h following the start of symptoms.
going BMT, the peak incidence of DAH in our patients was within the first 5 weeks of BMT, during the period of WBC count recuperation.

The clinical characteristics of our children match those described in similar reports. Hemoptysis in adults with DAH is not a common presenting symptom, but all six children in our current study had experienced hemoptysis early in the course of their illness, which is similar to what has been reported by Heggen et al. The radiographic abnormalities in our patients were nonspecific, with the findings consisting mostly of a mild interstitial or alveolar pattern in the central and lower lung zones. These findings are indistinguishable from pulmonary edema or opportunistic infection, which are other common complications after BMT.

The pathogenesis of DAH is poorly understood and probably multifactorial, with a common ultimate event involving a nonspecific injury to alveolar capillary endothelial membranes. One theory proposes that different pulmonary structures that have been partly damaged after chemotherapy and/or irradiation become more vulnerable to the toxic effects of neutrophils, which invade the lung causing pulmonary damage by their proteases and free radicals. Another suggested mechanism of injury involves an inflammatory cells-induced cytokine storm, occurring in the periengraftment period as the mediator of endothelial injury.

The role of thrombocytopenia in causing DAH is not entirely clear. Although it is present in most of the adult patients during the first weeks post-BMT, as it was in all our pediatric patients or those reported by Heggen et al., not all the patients who demonstrated thrombocytopenia develop DAH. Furthermore, platelet transfusions were not shown to improve the condition of the patients who had developed DAH.

In view of the common pathologic finding (i.e., nonspecific endothelial injury) and given their strong anti-inflammatory effect, it was assumed that the administration of glucocorticoids would blunt the inflammatory response that precedes DHA. As such, high-dose corticosteroid therapy was suggested for the treatment of DAH and has been reported to improve patients’ outcome. Yet five of our reported children died despite the high dose of methylprednisolone that we had administered. The acuteness and the fulminant nature of the disease entity in our patients might serve to explain this poor response.

The main limitation of our current analysis is that, due to its retrospective nature, only limited clinical information was collected during the course of the intensive care stay. In addition, there might have been selection biases and limitations in data accrual. Because of the rarity of this disease entity, we identified only six patients within a period of 6 years. Furthermore, we were unable to evaluate the role of steroids on patient outcome in a randomized well-controlled manner.

**CONCLUSION**

Being as it is a potentially fatal respiratory complication, DAH should be considered early in the differential diagnosis of acute respiratory failure in children following allogenic BMT for both nonmalignant and malignant diseases. When it occurs in infants, the prognosis is grim, and little benefit is gained from steroid treatment. Issues such as previous treatment with busulfan or lung shielding from irradiation need to be investigated further, as well as the apparent association between nonmalignant genetic diseases and DAH in pediatric patients undergoing BMT.

ACKNOWLEDGMENT: Esther Eshkol is thanked for editorial assistance.

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