Bronchiolitis Obliterans in Bone Marrow Transplantation and Its Relationship to Chronic Graft-v-Host Disease and Low Serum IgG

By H. Kent Holland, John R. Wingard, William E. Beschorner, Rein Sarai, and George W. Santos

The records of 549 bone marrow transplant (BMT) patients at The Johns Hopkins Oncology Center during a 9-year period were reviewed to determine the incidence of bronchiolitis obliterans (BrOb). Seven patients had BrOb. All seven died, and BrOb was a contributing cause of death in six patients. Only recipients of allogeneic BMT were at risk for developing BrOb (2% incidence). Three cases were incidentally discovered at autopsy in patients who died <120 days after BMT from ventilatory failure owing to interstitial pneumonitis. Four cases were patients who died >120 days after BMT. Of this latter group, all had overt chronic graft-v-host disease (CGVHD). Among 120 day survivors of allogeneic BMT, 6% of those with CGVHD developed BrOb as compared with none of those without CGVHD (P = .008). Five percent of patients with reduced IgG levels at day 120 developed BrOb as compared with none of those with normal IgG (P = .04). The incidence of BrOb in 120-day survivors was 14% (4 of 29) in patients with both CGVHD and decreased serum IgG, whereas patients with CGVHD only (0 of 28), those with decreased IgG levels only (0 of 53), and those with no CGVHD and normal IgG levels (0 of 70) did not develop BrOb.

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B RONCHIOLITIS obliterans (BrOb) was initially described in 1901 and has been associated with various clinical entities.2,3,4,5 Recently, BrOb was described in patients undergoing heart-lung and allogeneic bone marrow transplantation (BMT).3,4,5 BrOb causes destruction of small airways and is histologically characterized by granulation tissue plugs within the small airways, often extending into the alveolar ducts, or by complete destruction of the small airways by fibrosis.3,6

Clinical manifestations of BrOb include dyspnea and an unproductive cough. The etiologies for BrOb include a broad spectrum of injury to the lung, including pulmonary infections/organizing pneumonia (especially viral infections and mycoplasma infections), toxic inhalants, connective tissue diseases (most frequently rheumatoid arthritis), pulmonary alveolar proteinosis. Some cases have no identifiable cause.6-11 This study examined the incidence of BrOb in our BMT patient population and its relationship to the type of transplant, graft-v-host disease (GVHD), and serum immunoglobulins.

MATERIALS AND METHODS

From November 1976 to November 1985, 549 patients underwent BMT at The Johns Hopkins Hospital. The BMT preparative regimens, GVHD prophylaxis, and treatment have been cited previously.6-15 In general, patients with hematologic malignancies received one of two preparative regimens, consisting of busulfan and cyclophosphamide (Bu-Cy), or cyclophosphamide and total body irradiation (Cy-TBI). Patients with aplastic anemia received either Cy alone or Cy-TBI.20 Posttransplant immunosuppression was given for 6 months in recipients of allogeneic transplants to prevent GVHD. Generally this consisted of low doses of Cy, methotrexate (MTX), or cyclosporine-A (CSA). Some patients also received methyprednisolone (MP) along with either Cy or CSA. Patients who developed chronic GVHD (CGVHD) were treated with immunosuppressive therapy; generally, it consisted of prednisone and azathioprine. Immunoglobulin quantitations of IgG, IgA, and IgM were determined from sera using a rate nephelometer (Beckman Automated Immunochemistry System), and normal ranges were adjusted for age.6 The general management of these patients was described previously.15-17 Patients were advised of the risks of marrow transplantation and the attendant procedures and gave informed consent in accordance with the guidelines of the Joint Committee of Clinical Investigation of The Johns Hopkins Hospital and The Johns Hopkins University School of Medicine.

All clinical and autopsy records were reviewed to detect patients with BrOb pathologically or patients with progressive respiratory symptoms with at least moderate obstructive ventilatory defects by pulmonary function testing (which included the forced expiratory volume in 1 second (FEV1), the forced vital capacity (FVC), postbronchodilator spirometry, and flow-volume loops with helium isoflow breathing flow rate testing).20-22 A ratio of FEV1 to FVC expressed as a percentage was used to evaluate obstructive airflow. An FEV1/FVC value <70% was interpreted as moderate airway obstruction.20 Flow-volume loops with air and 80% helium were performed to exclude large airway obstruction.20,21 Patients with progressive clinical respiratory symptoms and obstructive ventilatory defects without corroborating pathologic examination were designated as having probable BrOb.20,21 Histopathologic criteria for BrOb were obliteration of the lumina of terminal and respiratory bronchioles owing to raised masses of edematous granulation tissue containing multiple fibroblasts.23 The bronchioles usually contained a mixed chronic inflammatory infiltrate in the surrounding alveoli (Fig 1). Lymphocytic bronchitis was assessed in the sections of mainstem bronchi taken distally to the carina and above the pulmonary hilum23; it was characterized by a pure lymphocytic infiltrate within the epithelium and submucosa, and frequent single cell necrosis of the epithelium. Interstitial pneumonitis (IP) was recognized by septal thickening due to septal edema or fibrosis, alveolar cell hyperplasia and, often, hyaline membranes.23 Diagnosis of CGVHD was made using published criteria by pathologic examination of skin, liver, minor salivary gland, or oral mucosal biopsies.24 The presence of immunoglobulin secretory cells in the gut secondary to GVHD and IgA and IgM containing plasma cells were evaluated. These techniques have been described previously.20,21 Postmortem cultures of the liver, spleen, and lung were performed for viruses on the following cell lines: WR-38, MRC-5, HEL-A, HEK.

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changes. Routine stains included Gram Weigert (for Pneumocystis), cultures were also performed on all specimens. Numerous sections of cytomegalovirus (CMV), herpes simplex virus (HSV), parainfluenza, and respiratory syncytial virus (RSV). Bacteria and fungal cultures were also performed on all specimens. Numerous sections of the lung were taken at autopsy and examined for viral cytopathic changes. Routine stains included Gram Weigert (for Pneumocystis), methenamine silver and periodic acid-Schiff (PAS) (for fungus), and Gram stain (for bacteria).

RESULTS

During this 9-year period, 549 patients underwent BMT: 386 patients were recipients of allogeneic transplants, 143 underwent autologous transplantation, and 20 had received syngeneic transplants. The demographic and treatment characteristics of these patients were described previously.27,28 Seven patients had BrOb (6 revealed by autopsy, and 1 by clinical criteria and pulmonary spirometry). All seven cases of BrOb occurred in the 386 allogeneic BMT recipients (an incidence of 2%). No cases were observed in the 163 patients who underwent autologous or syngeneic BMT.

BrOb cases. The demographic and treatment characteristics are outlined in Table 1. Four of the seven patients were male and three were female. The ages ranged from 4 to 26 years. There were four cases of BrOb (3%) in the 128 patients treated with Bu-Cy and 3 BrOb cases (2%) in the 190 patients treated with Cy-TBI. In six of the seven patients, the primary cause of death was pulmonary failure. One patient died of seizure. Four of the seven patients had received drugs known to cause pulmonary toxicity prior to transplantation. Only one of the seven patients (UPN no. 77) had BrOb who had a prior history of respiratory disease. This patient had a history of asthma. Pretransplant spirometry demonstrated a mild obstructive ventilatory defect, correctable to 80% of predicted FEV1/FVC vol by bronchodilators. By day 90 after BMT, the patient developed progressive dyspnea. Chest radiograph evaluations revealed no infiltrates or interstitial process. Spirometry, flow loops, and helium isoflow studies were done on day 186. Spirometry showed moderate obstructive ventilatory defect with no significant change with bronchodilators (FVC 41%, FEV1 19%, FVC/FEV1 45%). Flow volume loops were done with air (expiratory: V\text{max} 3.7 l/s, inspiratory: V\text{max} 2.5 l/s) and with 80% helium (expiratory: V\text{max} 3.8 l/s, inspiratory: V\text{max} 3.0 l/s (helium)). These studies did not suggest upper airway obstruction.31,32 The patient died on day 223 of irreversible respiratory failure.

Three patients developed an acute onset of ventilatory failure with a clinical picture consistent with IP. They had progressive respiratory failure within <4 weeks, dying at a median of 68 days after BMT. All three had clinical and pathologic evidence of acute GVHD. None of these patients had clinical evidence for CGVHD antemortem, but pathologic evidence of CGVHD was detected in two at autopsy. Patient UPN no. 77 died on day 102 and at autopsy had CGVHD of the liver and skin. Patient UPN no. 99 died on day 49 and had CGVHD of the liver.

Four patients had a later, more indolent onset of pulmonary symptoms with gradual ventilatory failure. These patients died at a medium of 252 days after BMT. Although three of these four patients also had IP, the episodes of IP were discrete and symptoms had resolved prior to the onset of BrOb. All four patients had markedly low serum IgG and IgA, and three of the four also had decreased IgM. The low levels of serum IgG preceded the onset of BrOb in three patients by 29 to 358 days and its fall of uncertain onset with relation to BrOb in one (Table 1; for UPN no. 349, the IgG level was not assayed from day 100 to day 276). All four patients also had clinical and histologic manifestations of CGVHD. The extent and severity of CGVHD was mild: three of the four patients had <25% of their skin involved by CGVHD. The CGVHD appeared after the onset of pulmonary symptoms in three of the four patients.

Tissue examination. Selected autopsy findings are shown in Table 2. Although BrOb was extensive in the six autopsy cases, other histologic pulmonary abnormalities were also noted. Of the three patients who died early,
Table 1. Demographic and Clinical Characteristics of Patients Who Developed BrOb

<table>
<thead>
<tr>
<th>UPN</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Previous Pulmonary Toxic Drugs</th>
<th>BMT Regimen</th>
<th>AOGHD Grade</th>
<th>CGVHD</th>
<th>IgG</th>
<th>Bacterial Fungal Pneumonia</th>
<th>Interstitial Pneumonia</th>
<th>Onset of Symptoms c/w BrOb</th>
<th>Death Idays s/p BMT</th>
<th>Primary Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>337</td>
<td>8</td>
<td>F</td>
<td>ALL</td>
<td>MTX/6-MP</td>
<td>Cy-TBI</td>
<td>0</td>
<td>—</td>
<td>Normal</td>
<td>No</td>
<td>Idiopathic day 40</td>
<td>40</td>
<td>68</td>
<td>Pulmonary failure</td>
</tr>
<tr>
<td>77</td>
<td>26</td>
<td>F</td>
<td>AML</td>
<td>Bleomycin/MTX</td>
<td>Bu-Cy</td>
<td>0</td>
<td>+ day 102</td>
<td>Low day 71</td>
<td>Bronchopneumonia day 64</td>
<td>Idiopathic day 86</td>
<td>86</td>
<td>102</td>
<td>Pulmonary failure</td>
</tr>
<tr>
<td>99</td>
<td>11</td>
<td>M</td>
<td>ALL</td>
<td>None</td>
<td>Cy-TBI</td>
<td>2</td>
<td>+ day 49</td>
<td>Low day 39</td>
<td>Bronchopneumonia day 37</td>
<td>Idiopathic day 30</td>
<td>30</td>
<td>49</td>
<td>Pulmonary failure</td>
</tr>
<tr>
<td>335</td>
<td>4.5</td>
<td>F</td>
<td>Acute myelofibrosis</td>
<td>None</td>
<td>Bu-Cy</td>
<td>2</td>
<td>+ day 111</td>
<td>Low day 42</td>
<td>No</td>
<td>Pneumocysis day 108</td>
<td>— 400</td>
<td>602</td>
<td>Seizure</td>
</tr>
<tr>
<td>547</td>
<td>15</td>
<td>M</td>
<td>ALL</td>
<td>MTX</td>
<td>Cy-TBI</td>
<td>2</td>
<td>+ day 172</td>
<td>Low day 73</td>
<td>Aspergillosis day 162</td>
<td>Idiopathic day 166</td>
<td>102</td>
<td>176</td>
<td>Pulmonary failure</td>
</tr>
<tr>
<td>349</td>
<td>18</td>
<td>M</td>
<td>AML</td>
<td>None</td>
<td>Bu-Cy</td>
<td>1</td>
<td>+ day 268</td>
<td>Low day 276*</td>
<td>Bronchopneumonia day 235</td>
<td>CMV day 102</td>
<td>120</td>
<td>280</td>
<td>Pulmonary failure</td>
</tr>
<tr>
<td>599</td>
<td>21</td>
<td>M</td>
<td>Hodgkins</td>
<td>Bleomycin/MTX</td>
<td>Bu-Cy</td>
<td>1</td>
<td>+ day 131</td>
<td>Low day 35</td>
<td>No</td>
<td>No</td>
<td>90</td>
<td>223</td>
<td>Pulmonary failure</td>
</tr>
</tbody>
</table>

AGVHD, clinical grade. Onset of symptoms c/w BrOb was associated with dyspnea and absence of pulmonary infiltrates (except in patients 1 and 3 in whom CXR abnormalities were present). IgG, data on which lg became low and remained low subsequently. CGVHD, data on which CGVHD was diagnosed by biopsy.

Abbreviation: c/w, consistent with; s/p, status post.

*Previous IgG serum level drawn on day 100.
lymphocytic bronchitis was observed in two (patients 77 and 99), and GVHD of the mainstem bronchi was observed in the third patient (UPN no. 337). Idiopathic IP was found postmortem in three patients. No findings suggested aspiration or reflux owing to esophageal stenosis in any of the patients.

The infectious agents found in the lung postmortem are listed in Table 2. In none of the patients were adenovirus, Coxsackie virus, HSV, parainfluenza virus, or RSV isolated by culture. Multiple histologic sections of the lung were examined; no evidence was found for viral infection except in one patient (UPN no. 349) who had CMV.

In none of the patients were salivary glands or lacrimal glands examined pathologically; however, none of the patients had evidence of sicca syndrome antemortem (one patient, UPN no. 547, had decreased tear production in one eye). Absence of immunoglobulin secretory cells in the gut resulting from GVHD was also sought in five patients. Two patients (UPN nos. 99 and 77) had depletion of the IgA and IgM containing plasma cells. Three other patients (UPN nos. 377, 349, and 547) showed a marked reduction in the number of intestinal plasma cells (Ig isotype was not studied).

Association of BrOb with demographic and patient characteristics in allogeneic BMT patients. Two of 58 patients aged 0 to 10 years (3%), 3 of 126 patients aged 11 to 20 years (2%), 2 of 107 patients aged 21 to 30 years (2%), 0 of 78 patients aged 31 to 40 years (0%), and 0 of 17 patients aged >40 years (0%) developed BrOb. None of these comparisons were statistically significant. BrOb occurred in 3 of 134 females (2%) and 4 of 252 males (2%) (P = NS). Six of 238 patients (3%) transplanted for acute leukemia, 1 of 16 patients (6%) with lymphoma, none of 90 with aplastic anemia, and none of 42 patients with CML developed BrOb (none of the comparisons were statistically significant).

The risk for BrOb was equivalent in patients receiving either Bu-Cy (4 of 128, 3%) or those given Cy-TBI (3 of 190, 2%) (P = NS). The survival rates of patients treated with either Bu-Cy (34 of 128, 27%) or Cy-TBI (56 of 190, 29%) was comparable, with a minimum follow-up of 18 months.

BrOb occurred in 5 of 139 patients given Cy (4%), 2 of 94 given CSA (2%), and none of 67 given MTX, none of 43 treated with CSA plus MP, and none of 40 patients given Cy plus MP as GVHD prophylaxis (P = NS).

Of the 386 allogeneic BMT patients, 166 (43%) developed IP (fatal in 147). Six of the 166 patients with IP had BrOb (4%), whereas only 1 of 220 (0.5%) without IP had BrOb (P = .03). Among patients who died, 6 of 147 (4%) patients with IP and 1 of 121 (1%) without IP had BrOb (P = NS). Among patients who were autopsied, BrOb was found in 6 of 117 patients with IP (5%) and 0 of 33 without IP (P = NS).

Association with CGVHD and serum immunoglobulins. The incidence of BrOb in allogeneic BMT patients with CGVHD (9%) greatly exceeded the incidence in those without CGVHD (0.03%, P = .02). Excluding patients who died early after BMT, and who thus did not live long enough to be at risk for developing CGVHD, no cases of BrOb occurred in 140 patients surviving ≥120 days without CGVHD as compared with four cases of BrOb in 62 patients (6%) with CGVHD (P = .008) (Table 3).

The relationship between BrOb and levels of serum immunoglobulins measured at day 120 after BMT was examined. Of the 202 patients who survived 120 days, IgA levels were low in 82 of 177 (46%) patients tested, IgA levels were low in 111 of 166 (67%) patients, and IgM levels were low in 56 of 165 (34%) patients tested. Patients with low levels of IgG were at greater risk for BrOb than those with normal IgG (P = .04), but there was no increased risk of BrOb in those with low IgA or IgM relative to patients with normal levels (P = .20 and P = .11, respectively).

There was a 14% incidence of BrOb in patients with both CGVHD and low serum IgG (Table 4). In contrast, none of the patients with CGVHD and normal IgG levels, none of

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**Table 2. Autopsy Findings in Addition to BrOb**

<table>
<thead>
<tr>
<th>UPN</th>
<th>GVHD</th>
<th>Mainstem Bronchi</th>
<th>Peribronchial Glands</th>
<th>Lungs</th>
<th>Infectious Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>337</td>
<td>Acute: skin, tongue, liver</td>
<td>GVHD with squamous metaplasia</td>
<td>Mild lymphocytic infiltrate with vasoconstriction</td>
<td>IP</td>
<td>Negative</td>
</tr>
<tr>
<td>77</td>
<td>Acute: tongue</td>
<td>Lymphocytic bronchitis</td>
<td>No significant changes</td>
<td>IP</td>
<td>Bronchopneumonia</td>
</tr>
<tr>
<td>99</td>
<td>Acute: skin, intestines</td>
<td>Lymphocytic bronchitis</td>
<td>Lymphocytic infiltrates, fibrosis</td>
<td>IP</td>
<td>Bronchopneumonia</td>
</tr>
<tr>
<td>335</td>
<td>Chronic: liver</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Negative</td>
</tr>
<tr>
<td>349</td>
<td>Chronic: skin, intestines</td>
<td>Mucosal fibrosis</td>
<td>Lymphocytic infiltrates, fibrosis, decreased goblet cells</td>
<td>Aspergillosis</td>
<td>Aspergillus fumigatus</td>
</tr>
<tr>
<td>547</td>
<td>Acute: skin</td>
<td>Lymphocytic bronchitis</td>
<td>Mild lymphocytic infiltrate, fibrosis decreased goblet cells, &quot;plugged&quot; ducts</td>
<td>Aspergillosis</td>
<td>Aspergillus fumigatus</td>
</tr>
</tbody>
</table>

NA, not available.

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**Table 3. Risk for Developing BrOb in All Allogeneic BMT Patients Surviving 120 Days With or Without CGVHD**

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of Patients</th>
<th>No. of Patients with BrOb</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGVHD</td>
<td>62</td>
<td>4 (6%)</td>
<td>0.008</td>
</tr>
<tr>
<td>No CGVHD</td>
<td>140</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
CGVHD as compared with 6% in patients who developed enough to be at risk for developing CGVHD, there were no autologous geneic BMT, with an overall incidence of 2%, sparing defects were also common at one cytobronchitis, which has been documented to be a sequela of study.23 Bronchitis has been associated with up to 13% of the cases of bronchiolitis, with a reported mortality of only 4%,16 of predicted values were not transplanted. Thus, significant pretransplant ventilatory impairment was excluded. However, some patients may have had subclinical preexisting small airway disease unrelated to the BMT. This appears unlikely since the pre-BMT characteristics (age, prior therapy, underlying hematologic disease) were similar in the two transplant groups. Furthermore, because all patients with late onset BrOb had a relentless downhill course that began after BMT, it probably did not predate BMT.

We found no statistically significant association of BrOb with age, sex, diagnosis, cigarette smoking, BMT preparative regimen, and GVHD prophylaxis. Clark and co-workers, by spirometry, noted an increased incidence of mild airflow obstruction in patients with CGVHD and in those given MTX for GVHD prophylaxis, but not in those treated with CSA.50 MTX prophylaxis was not used in the seven patients identified in this study, and BrOb was not noted in the 67 patients given MTX for GVHD prophylaxis. However, clinically inapparent or mild changes of PFTs associated with MTX would not have been identified in this retrospective review.

BrOb occurred in 6 of 166 (4%) patients with IP, and BrOb was noted in 1 of 220 (0.5%) patients without a history of IP (P = .03). The association of BrOb and IP in those patients who died or in those who were autopsied was not statistically significant. Because of the potential case selection bias, which may have missed less severe cases of BrOb, the latter comparisons may be more appropriate. Thus, until prospective studies are performed, the association of BrOb and IP must remain unclear.

BrOb was significantly associated with CGVHD, especially among 120-day survivors of BMT. The three “early” cases were detected in individuals without overt clinical evidence of CGVHD, but pathologic evidence of CGVHD was found at autopsy in two. Because BrOb generally predated CGVHD in the late-onset cases, it is very likely that with longer survival these patients would also have developed the clinical manifestations of CGVHD.

Table 4. Risk for Developing BrOb Among Allogeneic BMT Patients Surviving ≥120 Days in Relation to CGVHD and Serum IgG Level (at 120 Days)

<table>
<thead>
<tr>
<th>CGVHD</th>
<th>IgG*</th>
<th>No. Developing BrOb</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Low</td>
<td>4/29 (14%)</td>
<td>—</td>
</tr>
<tr>
<td>Yes</td>
<td>Normal</td>
<td>0/25</td>
<td>.08</td>
</tr>
<tr>
<td>No</td>
<td>Normal</td>
<td>0/70</td>
<td>.006</td>
</tr>
<tr>
<td>No</td>
<td>Low</td>
<td>0/53</td>
<td>.01</td>
</tr>
</tbody>
</table>

* Assayed at or after day 120.

those with low IgG and no CGVHD, and none of those without CGVHD and normal IgG levels developed BrOb.

DISCUSSION

Pulmonary complications are a frequent cause of morbidity and mortality in patients undergoing BMT. In the early posttransplant period (<100 days) the most notable syndromes are IP (occurring in 35% to 45% of all allogeneic BMT recipients) with a high mortality,27,28,34-42 and lymphocytic bronchitis, which is a manifestation of acute GVHD.35 Ventilatory abnormalities >100 days after BMT have also been noted.43-45 Restrictive impairment of ventilatory capacity is common. In one series, 21% of patients had reduced alveolar volume <89% predicted at 1 year after BMT.43 Obstructive ventilatory defects were also common at one year after BMT: 15% had a ratio of FEV₁/FVC <70%. At 3 years, 30% had this abnormality. Although the number of patients studied was small and the number of serial studies in individual patients was even smaller, there was a suggestion that obstructive airway disease may become more frequent with increasing time after transplant.

BrOb, one cause of obstructive pulmonary disease, is a rare condition in the general population and its cause is usually not determinable. Most patients improve with time, with a reported mortality of only 4%.16 Adenovirus infection has been associated with up to 13% of the cases of bronchiolitis in young children.19 In a beagle model, adenovirus caused a severe necrotizing and proliferative bronchitis and bronchiolitis, with a 50% reduction in bronchiolar cross-sectional area at 26 days after infection.46 RSV caused up to 43% of the bronchiolitis infections in children.47 RSV has also been reported to cause fatal pneumonia in immunocompromised patients.48 Autoimmune disorders, especially rheumatoid arthritis, have also been associated with BrOb.12 BrOb has also been described as a sequela of human heart-lung transplantation, occurring in 5 of 14 long-term survivors in one study.10 BrOb has been documented to be a sequela of allogeneic BMT.27 Several case reports have noted its occurrence in patients with CGVHD. Ralph and colleagues estimated that BrOb occurred in ~10% of long-term survivors with CGVHD.3

In this study, BrOb occurred only in recipients of allogeneic BMT, with an overall incidence of 2%, sparing autologous and syngeneic BMT recipients. Excluding patients who died early after BMT and thus did not live long enough to be at risk for developing CGVHD, there were no cases of BrOb in patients surviving ≥120 days without CGVHD as compared with 6% in patients who developed CGVHD (P = .008). Because prospective pulmonary function tests (PFTs) were not performed in all patients in this analysis and autopsies were performed in only 65% of those who died, this incidence is probably an underestimate. Patients with mild and nonlethal ventilatory defects would not have been included, as only patients with severe complications were identified. However, this is probably not a serious shortcoming, since spontaneous alleviation of severe symptoms owing to BrOb rarely occurs in immunocompromised patients (in contrast to sporadic viral bronchiolitis in the general population) and progressive symptomatology is the usual course.48 Similarly, symptoms without pathologic confirmation or obstructive ventilatory impairment were not counted in our review since other pulmonary syndromes (particularly interstitial pneumonitis) may have accounted for the patients’ symptoms.

Pretransplant PFTs were done routinely only in the cohort of autologous BMT patients. No patient of this group had preexisting obstructive ventilatory defects. Pretreatment PFTs in allogeneic BMT patients were done only in those with a history of respiratory problems or in those with lymphoma who had received thoracic irradiation. Patients with FEV₁ or FVC <75% of predicted values were not transplanted. Thus, significant pretransplant ventilatory impairment was excluded. However, some patients may have had subclinical preexisting small airway disease unrelated to the BMT. This appears unlikely since the pre-BMT characteristics (age, prior therapy, underlying hematologic disease) were similar in the two transplant groups. Furthermore, because all patients with late onset BrOb had a relentless downhill course that began after BMT, it probably did not predate BMT.

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CGVHD is an immunologic disorder with features resembling both autoimmune and collagen vascular diseases, with cellular and humoral immunodeficiency. The association of BrOb with CGVHD, heart-lung transplantation, collagen vascular diseases, and its known causation by viral infection in animal models suggests that the immunodeficiency caused by the CGVHD and/or its treatment may have made the patients more susceptible to occult respiratory pathogens, resulting in BrOb. An alternative hypothesis of the etiology of BrOb is an autoimmune process as part of CGVHD directed at the bronchiolar tree. Supporting this latter hypothesis is the observation in rats given lung allografts that induction of class II antigens on bronchial epithelial cells closely correlates with the rejection process.53

Although low IgG can be a manifestation of severe CGVHD, in the patients with BrOb the fall in IgG predated CGVHD by ≥2 months. The general temporal sequence of events in those patients surviving 120 days was a fall in IgG, followed by BrOb, and finally overt clinical manifestations of CGVHD. This sequence suggests that the IgG deficiency is either an early manifestation of CGVHD preceding its classical clinical manifestations or the IgG deficiency may predispose the patient to an infectious complication, as yet obscure, leading in some fashion to BrOb.

Immunoglobulin deficiency (especially of IgG and IgA) has been associated with ventilatory compromise. Umetsu and colleagues reported that children with selective IgG-subclass deficiencies had recurrent sinopulmonary infections.52 Bjorkander and associates reported that of 29 patients with low IgA levels, impaired ventilatory function occurred primarily in patients with concomitant IgG subclass deficiency (IgG2, IgG3), whereas IgA deficiency alone was rarely associated with respiratory illness.53 They also demonstrated that immunoglobulin prophylaxis reduced respiratory infections.

The postmortem histologic findings in five of the seven patients showing the absence of immunoglobulin secretory cells in the gut is suggestive of an extensive systemic and local humoral deficiency in these patients. Whether the occurrence of BrOb in allogeneic BMT patients is associated with abnormal local immunoglobulin secretory function in the lungs as well remains to be elucidated.

In conclusion, patients who undergo allogeneic BMT and develop CGVHD are at risk for BrOb. This risk is further associated with low serum IgG. Although the specific pathologic mechanism for developing small airway disease remains unknown in allogeneic BMT, early detection using ventilatory function tests and correction of IgG deficiency need study to determine their role in the prevention of progressive pulmonary failure.

REFERENCES

23. Tutschka PJ, Beschonner WE, Hess AD, Santos GW: Cyclo-


25. Elfenbein GJ, Mellits ED, Santos GW: From The Johns Hopkins Bone Marrow Transplant Program. Patients with aplastic anemia. Engraftment and survival after allogeneic bone marrow transplantation for severe aplastic anemia. Transplant Proc 15:1412, 1983


27. Wingard JR, Chen DY, Burns WH, Fuller DJ, Braine HG, Yeager AM, Burke PJ, Graham M, Santos GW, Saral R: Cyto-megalovirus infection after autologous bone marrow transplantation: Comparison to infection after allogeneic bone marrow transplantation (unpublished observations), 1987


41. Bamberg M, Beelen DW, Mahmoud HK, Molls M, Schaefer UW. The incidence of interstitial pneumonitis: Comparison of total body irradiation schedules for allogeneic bone marrow transplantation. Strahlenther Onkol 162:218, 1986

42. Winston DJ, Ho WG, Chamlin RE, Gale RP. Treatment and prevention of interstitial pneumonia associated with bone marrow transplantation, in Gale R (ed): Recent Advances in Bone Marrow Transplantation. Liss, New York, 1983, p 425


45. Wingard JR, Santos GW, Saral R: Late-onset interstitial pneumonia following allogeneic bone marrow transplantation. Transplantation 39:21, 1985


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