To the Editor:

We recently reported a relatively high cumulative incidence (26.1%) of obstructive lung disease (OLD) in children after allogeneic bone marrow transplantation (BMT). \(^1\) OLD in these children, histologically consistent with bronchiolitis obliterans, may be associated with severe respiratory insufficiency, leading to death in at least 30% of patients. Understanding factors that are associated with OLD in these children may contribute to improved therapy and survival. Gastroesophageal reflux (GER) in association with esophageal disease has been postulated as a cause of OLD in BMT patients. \(^1,2\) To test this hypothesis, we evaluated children with irreversible OLD for abnormal GER.

**Association of Gastroesophageal Reflux With Obstructive Lung Disease in Children After Allogeneic Bone Marrow Transplantation**
We identified 15 children with irreversible OLD after allogeneic BMT at British Columbia’s Children’s Hospital (1980-1992) and the Detroit Medical Center Bone Marrow Transplantation (1986-1992) Programs. The diagnosis of OLD was based on criteria previously described by our group. Patients diagnosed as having OLD showed no evidence of pulmonary abnormalities before transplantation. These patients had at least one of the following findings, in the absence of infection: (1) abnormal pulmonary function tests after transplant (FEV1 <80% predicted and FEF25-75% <60% predicted); (2) lung biopsy with evidence of fibrosis consistent with bronchiolitis obliterans; or (3) CT findings consistent with bronchiolitis obliterans. Diagnosis of GER was based on an abnormality of either (1) 24-hour pH probe and/or (2) upper gastrointestinal endoscopy with histologic evidence of esophagitis on biopsy. The 24-hour pH probe test was considered abnormal if the reflux index was greater than 6.0%.2

Of the 15 children with irreversible OLD, 11 were evaluated adequately for the presence of GER. We saw no significant difference in the patient characteristics of the children evaluated for GER and those who were not. The median age of the study patients was 4.7 years (range, 2.5 to 14.0 years) at the time of BMT. The sex ratio was 1.8:1 (M:F). Diagnoses of the BMT recipients included 5 with acute lymphoblastic leukemia, 2 with aplastic anemia, and 1 each with Fanconi’s anemia, chronic myelogenous leukemia, or acute myelogenous leukemia. Two children received an HLA-identical related donor, 4 an HLA-mismatched related donor, and 5 an HLA-matched unrelated donor. Total body irradiation (400 to 1,200 cGy) was administered in 7 of 11 of the children and methotrexate prophylaxis for graft-versus-host disease (GVHD) was administered in 9 of 11. All children had chronic GVHD, with all 11 classified as extensive. Diagnosis of OLD in children with abnormal GER was earlier (median, 9.1 months; range, 2.9 to 105.9 months) compared with those without (median, 33 months; range, 12.0 to 55.5 months). Eight of 11 (73%) children with established OLD had abnormal GER evident either by 24-hour pH probe test2 and/or abnormal esophageal histology6 (Table 1). Two of these children had esophageal stricture and one an inflammatory polyp at the gastroesophageal junction. In 4 of 8, the diagnosis of abnormal GER predated the diagnosis of OLD. Vomiting was apparent in 3 of 8 children with abnormal GER and in 1 without. Abnormal GER on radiologic evaluation was seen in 4 of 5 children evaluated. One child had lipid laden macrophages on bronchial alveolar lavage. Two of the 3 children without abnormal GER had strictures (1 small intestine and 1 esophagus) with normal histology at the time of testing. Ten of 11 children studied were able to perform pulmonary function tests (limited to children ≥5.0 years) and were evaluated at presentation or within 12 months after diagnosis of OLD. Of these children, the mean FEV1 was 40.3% predicted (95% confidence interval [CI], 26.7 to 53.9) in abnormal GER patients compared with 53.6% (95% CI, 20.5 to 86.7) in those without (P = .15), and the mean FEF25-75% was 31.8% in abnormal GER patients (95% CI, 2.4 to 61.2) compared with 54.3% (95% CI, 15.5 to 93.1) (P = .15). Both the FEV1 and FEF25-75% became worse over time in patients with abnormal GER, with no change in unaffected children. Of the 8 patients with abnormal GER, 4 died of respiratory failure and 1 secondary to relapsed disease. Three of the 4 children who died from respiratory failure underwent an autopsy. All had severe esophagitis and ulcerations. All of the patients without abnormal GER are alive.

We observed abnormal GER in 73% (8/11) of children with OLD after allogeneic BMT. In addition, 1 of the 3 children with OLD who were classified as unaffected for abnormal GER had esophageal strictures that may suggest previous episodes of GER. Although we do not know the incidence of abnormal GER in children without OLD after BMT, we think the children in this study had a high incidence of abnormal GER. Children who had abnormal GER also had a poor prognosis. Some of the children clearly had abnormal GER before the diagnosis of OLD, although many were diagnosed with abnormal GER at a later time. Whether GER worsens OLD is difficult to establish because both OLD and GER may make the other worse. Bronchiolitis obliterans may develop secondary to chronic aspiration of refluxed gastric fluids or by a neurally mediated reflex bronchoconstriction secondary to irritation of esophageal mucosa.4 However, OLDs, including cystic fibrosis,2 asthma,3 and infant bronchopulmonary dysplasia,4 can lead to abnormal GER. Antireflux medication intervention appears to result in significant improvement of lung disease in some patients with asthma or cystic fibrosis.8,9

At present, these data only suggest a causal relationship between abnormal GER and OLD in children after allogeneic BMT. A large prospective study with planned sequential evaluations for GER in children who develop OLD and controls is required. This study would clearly establish whether GER is causal for the development of OLD or secondary to OLD and establish the incidence of abnormal GER in children unaffected by OLD. Until these data are available, we recom-

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**Table 1. Evaluation for Abnormal GER in Children With OLD After Allogeneic BMT**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Vomiting</th>
<th>pH Probe</th>
<th>Endoscopic Findings</th>
<th>Esophageal Histology</th>
<th>Radiological GER Study</th>
<th>Manometry</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal GER</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Absent</td>
<td>Abnormal</td>
<td>GE junction polyp</td>
<td>Esophagitis</td>
<td>ND</td>
<td>Normal</td>
<td>Alive</td>
</tr>
<tr>
<td>2</td>
<td>Absent</td>
<td>Abnormal</td>
<td>ND</td>
<td>Esophagitis</td>
<td>ND</td>
<td>ND</td>
<td>Relapse</td>
</tr>
<tr>
<td>3</td>
<td>Absent</td>
<td>Abnormal</td>
<td>Esophagitis/ulcerations/stricture</td>
<td>Esophagitis</td>
<td>ND</td>
<td>Normal</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>4*</td>
<td>Present</td>
<td>ND</td>
<td>Esophagitis</td>
<td>Esophagitis</td>
<td>Abnormal</td>
<td>ND</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>5</td>
<td>Present</td>
<td>Abnormal</td>
<td>Esophagitis/ulcerations</td>
<td>Esophagitis</td>
<td>Abnormal</td>
<td>ND</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>6</td>
<td>Present</td>
<td>ND</td>
<td>Esophagitis</td>
<td>Esophagitis</td>
<td>Abnormal</td>
<td>ND</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>7</td>
<td>Absent</td>
<td>ND</td>
<td>Esophageal stricture</td>
<td>Esophagitis</td>
<td>Abnormal</td>
<td>ND</td>
<td>Alive</td>
</tr>
<tr>
<td>8</td>
<td>Absent</td>
<td>Abnormal</td>
<td>ND</td>
<td>ND</td>
<td>Normal</td>
<td>ND</td>
<td>Alive</td>
</tr>
<tr>
<td>No GER</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Absent</td>
<td>ND</td>
<td>Stricture small intestine</td>
<td>Normal</td>
<td>Abnormal</td>
<td>ND</td>
<td>Alive</td>
</tr>
<tr>
<td>10</td>
<td>Absent</td>
<td>ND</td>
<td>Normal</td>
<td>Normal</td>
<td>ND</td>
<td>Normal</td>
<td>Abnormal</td>
</tr>
<tr>
<td>11</td>
<td>Present</td>
<td>Normal</td>
<td>Severe esophageal stricture</td>
<td>ND</td>
<td>ND</td>
<td>Normal</td>
<td>Alive</td>
</tr>
</tbody>
</table>

Abbreviation: ND, not done.

* Patient had lipid laden macrophages on bronchial alveolar lavage.
recommend that children who develop chronic GVHD after allogeneic BMT be evaluated routinely for OLD at 3 and 12 months post-BMT and, if OLD is identified, that they receive a thorough work-up for GER. Because neither the symptom of vomiting nor radiologic evaluation for GER were sensitive in identifying abnormal GER, there should be a low threshold for evaluation of GER using 24-hour pH probe or endoscopy in any child who develops extensive chronic GVHD.

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REFERENCES


Association of gastroesophageal reflux with obstructive lung disease in children after allogeneic bone marrow transplantation [letter]

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