Bronchiolitis Obliterans in Single-Lung Transplant Recipients*

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The presentation and clinical course of bronchiolitis obliterans (BO) in single-lung transplant (SLT) recipients has thus far not been well described. We retrospectively analyzed the serial spirometry of 15 SLT patients with BO. All the patients fulfilled the criteria for BO syndrome, and 11 of the 15 had histologically documented BO. Based on serial FEV₁ analysis, we identified three patterns of presentation and progression of BO. The first pattern (n=6) was characterized by a rapid onset and a relentless progressive course; the second pattern (n=5) was characterized by a similar rapid onset and initial rapid decline, but was followed by stabilization in lung function; the third pattern (n=4) was characterized by an insidious onset and course. In all patients, a permanent reduction in the mean forced expiratory flow during the middle half of the forced vital capacity appeared to be an early sensitive index for the development of BO. An appreciation of these different modes of presentation and progression of BO is potentially important in the assessment of prognosis and management of the SLT recipient.

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Bronchiolitis obliterans (BO) has become the major complication impacting on long-term survival in lung-transplant recipients. It is thought to be immunologic in origin and the pathologic correlate of chronic rejection. This association was first recognized in the early 1980s in heart-lung recipients. With the evolution of thoracic organ transplantation from heart-lung to bilateral and single-lung transplantation, there has been a growing appreciation of the occurrence of BO in recipients of all lung allografts. The incidence of BO ranges from 10 to 50%. The mortality rate is not well established and has variably been reported at between 29 and 50%. The BO can be patchy in distribution and the obliterated bronchioles may be difficult to identify histologically. This can make it an elusive diagnosis to establish histologically with transbronchial biopsy (TBB). The sensitivity of TBB for BO ranges from 5 to 87%. Reliance on clinical criteria for the diagnosis of BO is rapidly gaining acceptance, and definition of a BO syndrome based on persistent significant decrements in the FEV₁ recently has been proposed.

The course of BO in single-lung transplant (SLT) recipients, as assessed via serial spirometry, however, has not as yet been described. We have noted spirometric variations in the presentation and progression of our SLT patients who have developed BO. The spirometric patterns of 15 SLT recipients who have BO syndrome with or without histologically documented BO form the basis of this analysis.

Methods

Clinical Data

Over a period of 4 years, we performed 37 adult SLTs. Postoperative immunosuppression consisted of induction immunosuppression in the immediate postoperative period with either OKT3 (5 mg/d), Minnesota anti-lymphocyte globulin, or antithymocyte globulin (ATG) (15 mg/kg/d) for 5 to 7 days. Maintenance immunosuppression therapy consisted of triple-drug therapy with cyclosporin A, azathioprine (1 to 2 mg/kg/d), and prednisone (tapered to a daily dose of 5 to 15 mg/d). Cyclosporin A whole blood trough levels were maintained in the 400 to 600 ng/mL range in the early postoperative period and in the 300 to 500 ng/mL range on a long-term basis (polyclonal TDX assay, Abbott). Azathioprine was adjusted to maintain the WBC count between 4,000 and 6,000 cells/mm³. All patients underwent routine spirometry with every clinic visit. Clinic visits were scheduled on a weekly basis initially, with subsequent tapering in frequency according to each individual patient’s progress. All patients were seen as clinically indicated or at least 3- to 6-month intervals. A 10 to 15% decrease in the patient’s home spirometric indexes constituted a clinical indication for an unscheduled clinic visit. Bronchoscopy with TBBs were per-
formed for clinical indications only. Between six and ten TBBs were performed with each bronchoscopy. All specimens were examined by the same pathologist. Aside from routine hematoxylin and eosin staining, Masson’s trichrome stain was performed on specimens from all bronchoscopies.

The serial spirometric indexes and arterial blood gas values of those patients with BO syndrome were examined retrospectively. The BO syndrome was defined as a permanent 20% decrement in the FEV₁ from the baseline value. Baseline spirometry was defined as the average of the spirometric indexes from the two posttransplant spirometries with the highest FEV₁ values that were separated by a period of at least 3 weeks. The spirometric indexes recorded included the forced vital capacity (FVC), FEV₁, mean forced expiratory flow during the middle half of FVC (FEF25-75%), and the FEV₁ to FVC ratio. Results for the FVC, FEV₁, and FEF25-75% are expressed as percentages of the predicted values for the recipients using the prediction formulas of Schmidt et al. All decrements were calculated from baseline unless otherwise stated. Rates of decrement were calculated over the period of time from when there was first evidence of an irreversible decrement to either a new stable baseline or to the latest FEV₁ in the case of continuous linear decrements.

The serial FEV₁ values expressed as percentages of predicted were plotted against time for each patient. These plots were examined by three of the authors (S.D.N., S.S., J.D.E.) for identification of distinct patterns of decline. Once patterns had been characterized, the 15 individual plots were given to three independent clinicians for classification of each plot.

The same criteria that were applied to the FEV₁ were used to define a baseline for the FEF25-75%. The point at which an irreversible 20% decrement from this baseline was reached was noted in each case. The highest room air PaO₂ before the onset of BO syndrome was recorded in all patients, and this was compared with the highest room air PaO₂ after the onset of BO syndrome where available. The PaO₂ that was available immediately prior to the onset of BO syndrome also was recorded to assess whether hypoxemia predated the onset of the BO syndrome.

Comparison was made of the baseline spirometry and spirometry at the onset of BO syndrome in each primary disease group and between patients having different patterns of decline. An assessment of the effect of cytolytic therapy and steroids given in bolus form was attempted by noting on the plots the point in time at which patients received therapy.

Statistical Analysis

Comparisons between groups with varying patterns of decline were made using one-way analysis of variance. The Student’s t-test was used when comparison was made between the COPD and idiopathic pulmonary fibrosis (IPF) patients.

RESULTS

Of the 26 SLT recipients who survived longer than 6 months, 15 have developed BO syndrome. The diseases for which these 15 patients were initially transplanted included the following: pulmonary fibrosis (7); COPD (5); sarcoidosis (1); primary pulmonary hypertension (PPH [1]); and lymphangioleiomyomatosis (1). Patient characteristics are shown in Table 1. Of the 15 patients, 11 have histologically proven BO. Of the histologically proven, 6 were documented with TBB, 2 with open-lung biopsy, and 3 at autopsy. In one of the patients, BO was documented histologically (via TBB) 2 months prior to the
onset of BO syndrome. A total of 41 bronchoscopies were performed after the onset of BO syndrome in the remaining 14 patients. Twenty nine of these were performed in the ten patients in whom a histologic diagnosis of BO was ultimately attained. The sensitivity of bronchoscopy with TBBs for BO after the onset of the BO syndrome was, therefore, 17% (5 of 29). At the time of histologic diagnosis of BO, there was no evidence of other potential causes of BO such as infection or aspiration.

Three distinct patterns of decrement in the FEV₁ were identified. The first pattern was characterized by a rapid onset and relentless progressive course. The second pattern was characterized by a similar rapid onset and initial rapid decline but was followed by stabilization in lung function. The new lower baseline (after the initial sharp decrement) was defined by the first FEV₁ after stabilization of loss of lung function was evident. The third pattern was characterized by an insidious onset and course.

Concordance of pattern recognition among the three clinicians was 100%. Six of the patients were characterized as having pattern 1 (group 1), four as having pattern 2 (group 2), and five as having pattern 3 (group 3). The BO was documented histologically in 6 of 6 patients in group 1, 2 of 4 in group 2, and 3 of 5 in group 3. The progressive decrement in the FEV₁ for all patients in each group can be seen in Figures 1 through 3. Baseline spirometry values of the three groups are shown in Table 2.

The mean time to onset of clinical BO was 12 months in group 1 (range, 3 to 22 months), 15 months in group 2 (range, 6 to 31 months), and 30 months in group 3 (range, 13 to 38 months); the probability value was 0.016. In the latter group, however, the start of loss of lung function was identified by an inflection point on the XY plots at 19 months (range, 9 to 24 months). The time to the irreversible 20% decrement in the FEF25-75% preceded the onset of the BO syndrome as defined by the FEV₁ in 12 of the 15 cases. In the remaining 3 cases, the 20% reduction in
the FEV₁ and FEF25-75% occurred simultaneously. All 3 of these patients were in group 2. The remaining patient in group 2 experienced the irreversible 20% FEF25-75% decrement 3 months before the onset of clinically evident BO. The irreversible decrement in the FEF25-75% predated the onset of the BO syndrome by 3 months in group 1 (range, 17 days to 5 months) and by 15 months in group 3 (range, 4 to 29 months). There was a mean decrease of 65% in the FEF25-75% at the time of diagnosis of the BO syndrome. This decrease was not significantly different among the three groups. The highest PaO₂ values preceding and after the syndrome are shown in Table 1. In only two patients did the onset of significant hypoxemia (defined as a decrease of 10 mm Hg from the highest PaO₂) precede the onset of BO as defined by the reduction in the FEV₁. One of the patients was the patient with PPH who was in group 1 (PaO₂ decreased from 71 to 52 mm Hg) and the other patient was a COPD patient in group 2 (PaO₂ decreased from 91 to 67 mm Hg). After the development of the BO syndrome, most of the patients did manifest varying degrees of hypoxemia.

In group 1, the patients had a mean decrement in the FEV₁ of 44% (range, 23 to 73%) from their stable baselines over a period of 7 months (range, 3 to 12 months). The initial sharp decrement in FEV₁ in group 2 occurred at a similar rate with the patients losing 46% of their baseline FEV₁ values (range, 21 to 74%) over a mean period of 7 months (range, 6 to 9 months). During the subsequent period of stabilization in group 2, the mean decline in FEV₁ was 3% from the post-initial sharp decline baseline. This period of stabilization has been evident for a mean period of 9 months (range, 2 to 16 months). None of these patients have had any subsequent periods of sharp decline in the FEV₁. In group 3, the loss of 20% in the FEV₁ that defined the onset of the BO syndrome occurred over a mean period of 11 months (range, 4 to 18 months). After the onset of the BO syndrome in this group, the rate of loss of FEV₁ was 11% (range, 6 to 18; n=3) over 10 months (range, 8 to 14 months; n=3) from the initial baseline value.

Five of the six patients in group 1 have died a mean of 6.5 months after the onset of the BO syndrome (range, 4 to 10 months). The one surviving patient had his initial decrement in FEV₁ only 3 months ago. All five of these patients died from progressive respiratory failure. In addition to BO, two of these five patients had evidence of pulmonary emboli at autopsy. One of the four patients in group 2 died 28 months after her initial decrement in FEV₁, from complications related to cytomegalovirus colitis. The other 3 patients are on average 14 months out from the onset of their initial sharp decrement (range, 8 to 18 months). One of the five patients in group 3 died from post-transplant lymphoproliferative disorder and renal failure related to aminoglycoside therapy. This occurred 25 months after the onset of decline in the FEV₁ level. Neither this patient nor any of the other patients in this group manifested any evidence of sharp declines in the FEV₁ values. The surviving patients in this group are on average 18 months beyond their initial onset of decline in lung function (range, 9 to 24 months).

In terms of therapy for BO, 13 of the 15 patients received at least one course of pulsed solumedrol after the onset of BO syndrome (1 g administered intravenously daily for 3 days). A total of 21 such pulses were administered. Four of these pulses appeared to result in a transient increase in the patients’ lung function (as defined by an increase in the FEV₁ of at least 10% within 1 month of the therapy). However, in only 1 of these 4 instances did the effect last longer (6 months) than 1 month. In addition to the pulsed solumedrol, six of the patients received a 10-day course of ATG (15/mg/kg/d) and one patient received a 10-day course of OKT3 (5 mg/day). Only three of the patients received these cytolytic agents during the serial monitoring of their spirometry values. Two of these patients were in group 2, and in both cases the initiation of therapy appeared to coincide with the point of inflection that characterized the transition from rapid decline to stabilization. The other patient was in group 3, and the course of ATG did not appear to impact on the rate of decline in this patient. Of the other four patients who received ATG, two received their courses during the terminal phases of their illness and the other two have only recently completed their courses.

Because of the small numbers, comparison of the spirometries of only the COPD and IPF patients was made. Baseline spirometry and spirometry at the onset of the BO syndrome are recorded in Table 3. All the spirometric indexes except the FEV₁, both at baseline and at the onset of the BO syndrome, were significantly different between the two groups. However, there was no difference in the percentage magnitude of the change in the FEF25-75%, FVC,

### Table 2—Baseline Spirometry Values in the Three Groups of Patients*

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline Spirometry Values</th>
<th>FVC</th>
<th>FEV₁</th>
<th>Ratio</th>
<th>FEF25-75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>63±5.4</td>
<td>61±3.3</td>
<td>82±4</td>
<td>56±9.8</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>83±8</td>
<td>69±4</td>
<td>69±5.9</td>
<td>32±3.8</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>72±7.6</td>
<td>67±6.5</td>
<td>78±4.3</td>
<td>47±7.6</td>
</tr>
</tbody>
</table>

*Numbers are expressed as percentage of predicted except the ratio which is expressed as percentage (±SEM). The probability value was not significant for all indexes.
and the FEV₁ to FVC ratio that accompanied the 20% decrement in the FEV₁.

DISCUSSION

By analyzing the serial spirometry of a group of SLT recipients with BO, we have characterized the onset and progression of BO. The patients may present in one of two ways: either suddenly or insidiously. These two patterns of presentation have previously been reported in heart-lung and lung transplant recipients. These patients who presented insidiously continued to progress in this fashion with none of the five patients in this group manifesting increased rates of decrement in lung function subsequently. The onset of disease also appeared to be at a later stage of their postoperative course than those patients who manifested with sudden decrements in lung function. The course of those patients in whom a sudden decrement in lung function heralded the onset of BO was variable. In those patients who constituted group 1, the rate of loss of lung function was unremitting, and 5 of these 6 patients have died a mean of 6.5 months after the onset of the BO syndrome. In those patients that constituted group 2, the initial sharp decrement was followed by stabilization of lung function after a period of time. The percentage and rate of loss of lung function before the period of stabilization in group 2 was similar to that in group 1. Subsequent to stabilization of lung function in group 2, the rate of decline did not appear to be significant; however, this is equally likely to be due to the brevity of follow-up at this time.

In all cases, a 20% reduction in the FEF25-75% preceded or occurred concurrently with the 20% decrement in the FEV₁. As with heart-lung recipients, our data suggest that a persistent reduction in the FEF25-75% may be the earliest indicator of BO in single-lung recipients. The specificity of this parameter, however, remains to be determined. Although the baseline percentage predicted FEF25-75% was lower in the COPD group of patients, the percentage reduction in this parameter at the onset of the BO syndrome was the same as that in the IPF group.

The nature of the contribution of the native lung to the spirometric pattern is the reason for the differences in the baseline spirometric indexes of our COPD and IPF patients. Aside from pathology in the allograft, serial spirometry in SLT recipients also may be affected by differing sequential emptying of the two sides or, conceivably, progression of disease on the native side.

In 13 of the 14 patients whose primary disease did not include PPH, significant hypoxemia did not predile the onset of the BO syndrome as defined by the reduction in the FEV₁. In the one patient with PPH, significant hypoxemia did predile the reduction in flow rates. The etiology of this is the marked ventilation-perfusion inequality that can result in this group of patients with any parenchymal process of the transplant side. This is due to the high fixed pulmonary vascular resistance of the native lung which precludes any concurrent shifts of perfusion with shifts in ventilation to the native side. We have one additional SLT recipient with PPH who has developed hypoxemia; however, as yet she has not manifested any reduction of flow rates. The clinical suspicion is that this patient too has early BO. These two cases underscore the possibility that persistent hypoxemia may be a more sensitive index of BO in patients with pulmonary vascular disease. The sensitivity of TBBs for BO after the onset of the BO syndrome was 17%, which is at the low end of the wide range that has previously been reported in the literature. This underscores the value of using clinical criteria, without histologic verification, for the diagnosis of a BO syndrome.

Whereas bolus doses of solumedrol are very effective in reversing episodes of acute rejection, at best using such therapy was a short temporizing measure in a small percentage of our patients with the BO syndrome. On the other hand, despite our small numbers, it is interesting to speculate on the possible ameliorating effects of cytolytic therapy. In 2 of the group 2 patients, stabilization of loss of lung function did appear to coincide with the administration of this therapy. A salutory response to augmented immunosuppression previously has been reported in both heart-lung and lung transplant patients. However, the association may have been coincidental, and indeed, two of the patients in group 2 did develop a plateau of loss of lung function without the benefit of
any additional therapeutic interventions.

Aside from the distinctive patterns of presentation and subsequent progression, the prognosis among the groups differs. All of the patients in group 1 were oxygen-dependent after 9 months, and none of them survived more than 13 months beyond their initial presentation. All of these patients died from progressive respiratory failure. Patients in groups 2 and 3 tended to have a more protracted course and, thus far, a lower mortality rate. Interestingly, the cause of death in these groups was not progressive respiratory failure. None of the deaths were believed to be related to the administration of augmented immunosuppressive therapy.

To our knowledge, this is the first in-depth report of the presentation, course, and prognosis of BO in SLT recipients. As with heart-lung recipients, the FEF25-75% appears to be a sensitive early indicator of BO in all SLT recipients. Hypoxemia may predate the onset of airflow obstruction in the subgroup of patients with pulmonary vascular disease. BO may have an acute or insidious onset and may occur at any time beyond the first few months of transplantation. The course of progression tends to mirror the nature of the initial presentation, although there is a subgroup of patients with acute onset, rapidly progressive BO who subsequently develop stabilization of their lung function. These distinct clinical patterns of BO may have immunopathogenetic correlates, with class 2 antigen-directed reactivity having been shown to be associated with a less aggressive clinical course than class 1 antigen-directed reactivity.

An appreciation of these patterns of presentation and progression are important in the early diagnosis and in determining the prognosis of SLT patients who develop BO. Consideration of these patterns also will be important in the design and implementation of future therapeutic salvage protocols.

REFERENCES