Role of Open Lung Biopsy for Diagnosis in Lung Transplant Recipients: Ten-Year Experience

Cecilia Chaparro, MD, Janet R. Maurer, MD, Dean W. Chamberlain, MD, and Thomas R. Todd, MD

Lung Transplant Program, Departments of Medicine, Pathology, and Thoracic Surgery, University of Toronto, and The Toronto Hospital, Toronto, Ontario, Canada

Between November 1983 and August 1993, The Toronto Lung Transplant Program performed 153 transplantations in 144 recipients: 53 single-lung transplantations (SLT) and 100 double-lung transplantations (DLT). Thirty-eight open lung biopsies (OLBs) were done in 32 (22% of all recipients): 19 in SLT (36% of SLT) 12 in DLT (12% of DLT), and 1 in a patient who had a SLT and then a double retransplantation. Six recipients underwent OLB twice: 1 DLT, 3 SLT, and 2 who had OLB both before and after retransplantation. Indication for 11 early OLBs (≤45 days postoperative) was persistent parenchymal infiltrates. Indications for 27 late OLBs (>45 days postoperative) included progressive radiologic disease with clinical findings or progressive loss of pulmonary function (18), persistent poor graft function (3), mass or nodules (3), persistent infiltrates without functional loss (2), and persistent lymphocytosis in bronchoalveolar lavage (1). Open lung biopsy confirmed a previous clinical or pathologic diagnosis in 11, suggested a diagnosis in 2, yielded nonspecific information in 16, and provided different diagnosis in 9. New diagnosis that changed therapy was made in 1 of 11 early OLBs and in 8 of 27 late OLBs. These 9 diagnoses included in SLTs: bronchiolitis obliterans (2), bronchiolitis obliterans organizing pneumonia (1), malignant lymphoma (1), and chronic vascular rejection (1) in SLT, and bronchiolitis obliterans organizing pneumonia (3) and *Burkholderia cepacia* infection (1) in DLT. We conclude that OLB is of little value in the perioperative period but yields useful information in approximately 30% of patients when performed late.

(Ann Thorac Surg 1995;59:928–32)

As the success of lung transplantation has increased, a wide range of pulmonary complications has been recognized. These complications often require a quick and safe procedure to establish a diagnosis.

The preferred route for investigation of pulmonary complications is bronchoscopy. Transbronchial biopsy (TBB), used in surveillance of these patients or in cases of acute clinical deterioration, has been shown to detect occult rejection or infection with high specificity and sensitivity, [1–3] especially when combined with bronchoalveolar lavage (BAL). However, occasionally clinical settings arise in which symptoms and noninvasive studies, pulmonary function tests, and chest radiographs suggest lung pathology but bronchoscopy or transthoracic needle biopsy fails to establish a diagnosis. In addition, rapid deterioration of a patient's condition may demand a faster and safe method to establish a diagnosis than could be reliably provided by minimally invasive procedures. In these cases open lung biopsy (OLB) may be necessary. We decided to review the OLB results in our lung transplant population over the past 10 years to gain a better understanding of its value in diagnosis and to determine its morbidity.

Accepted for publication Dec 24, 1994.

Address reprint requests to Dr Maurer, The Toronto Hospital, 200 Elizabeth St, EN10-220, Toronto, ON, Canada M5G 2C4.

Material and Methods

Design

We conducted a retrospective chart and pathology review of all OLB procedures performed in a population of 144 lung transplant recipients over a 10-year period.

Patients

Between August 1983 and November 1993 The Toronto Lung Transplant Program performed 153 transplantations in 144 recipients: 53 single-lung transplantations (SLTs) and 100 double-lung transplantations (DLTs). We identified those patients who had undergone OLB at any time after transplantation. We reviewed the clinical histories of each of these patients with particular emphasis on clinical presentation, pulmonary function, radiologic alterations, timing of the procedure relative to change in clinical status and other invasive procedures (eg, bronchoscopy), time of the procedure after transplantation, complications of OLB, survival after the OLB, pathology results, and influence on treatment decisions.

Indications for transplantation in this group of patients were as follows: pulmonary fibrosis (9), eosinophilic granuloma (5), α_1-antitrypsin deficiency (2), primary pulmonary hypertension (3), emphysema and bronchiolitis obliterans (1), scleroderma (1), sarcoidosis (1), and extrinsic allergic alveolitis (1), cystic fibrosis (5), bronchiolitis obliterans (BO) (1), emphysema (1), bronchiectasis (1), and Eisenmenger's syndrome (1) in the DLT group.

0003-4975/95/$9.50
0003-4975(95)00015-D

Definitions

Patients were divided, arbitrarily before reviewing the data, into two groups according to the time of OLB after transplantation: early OLBs were those performed within the first 45 days; and late OLBs were those biopsies performed more than 45 days after the operation.

Biopsies, preservation, surgical technique, surveillance protocol, immunosuppression, and infection prophylaxis have been described previously [4, 5]. All specimens obtained by OLB were reviewed by the same pathologist who also reviewed all TBBs.

Results

Between August 1983 and November 1993 The Toronto Lung Transplant Program performed 38 OLBs in 32 of 144 transplant recipients (22% of all recipients); of those, 19 had SLT (36% of all SLTs), 12 had DLT (12% of all DLTs), and 1 patient had an SLT and then a retransplantation DLT.

Indications for Open Lung Biopsy

All early OLB patients had radiologic evidence of pulmonary infiltrates, and clinical compromise manifested by either or both of (1) inability to be weaned from mechanical ventilation after transplantation or (2) persistent posttransplantation cough, fever, shortness of breath, or sepsis.

Among patients in the late OLB group several subgroups were identified that constituted indications for OLB. These were as follows:

ACUTE OR PROGRESSIVE PULMONARY DISEASE AND CLINICAL FINDINGS. Open lung biopsy was performed in this group whenever acute rapid or progressive deterioration occurred and was usually associated with pulmonary function and radiologic abnormalities.

PROGRESSIVE LOSS OF PULMONARY FUNCTION. Patients in this group had slow functional deterioration measured by exercise and pulmonary function studies without acute clinical compromise, symptoms or radiologic abnormalities.

RADIOLOGIC COMPROMISE WITHOUT CLINICAL FINDINGS. These patients had progressive radiologic abnormalities without pulmonary function test changes or clinical findings.

PERSISTENT POOR GRAFT FUNCTION. Included in this category were a few patients who never were well either functionally or clinically after their transplants, but who did not have perioperative biopsies.

PERSISTENT LYMPHOCYTOSIS IN BRONCHOALVEOLAR LAVAGE. Biopsy was performed in 1 patient with persistent elevation of BAL lymphocytes to more than 40% but with minimal histologic evidence of rejection and no symptoms or pulmonary function test abnormalities.

Indications for OLB are shown in Table 1. Early OLBs were performed 4 to 38 days after operation for SLT and 30 to 45 days after operation for DLT. Late OLBs for acute or progressive pulmonary disease and clinical findings were done between 3 and 7 months for SLT and 2 and 53 months for DLT. Biopsies performed for progressive loss of pulmonary function were done in 2 patients at 7 and 58 months after transplantation; OLBs for radiologic compromise without clinical findings were done between 3 and 6 months after transplantation, for persistent poor graft function in 3 patients between 3 and 5 months after operation, and for persistent BAL lymphocytosis in a patient 11 months after transplantation.

Table 1. Indications for Open Lung Biopsy

Indication	SLT	DLT	Total
Early OLB			
Perioperative period	7	4	11
Late OLB			
Acute or progressive disease	9	7	16
Loss of pulmonary function	2	...	2
Radiologic compromise	3	2	5
Lymphocytosis on BAL	...	1	1
Never well	3	...	3
Total	24	14	38

BAL = bronchoalveolar lavage; DLT = double-lung transplantation; OLB = open lung biopsy; SLT = single-lung transplantation.

Six recipients underwent OLB a second time. These included 2 with DLT and 4 with SLT. In all of them the repeat biopsy was done because the first was nonspecific or only suggested a diagnosis. In 4 the biopsies were repeated for the same indication. Of the 4, in 2 patients the repeat biopsy made a diagnosis of PTLD after the first biopsies were nonspecific or "suggestive"; a third patient had two biopsies demonstrating chronic vascular rejection, and the fourth patient had two nondiagnostic biopsies. The remaining 2 patients were patients who received retransplants and who had OLBs done in both the initial and retransplants for different indications. In each biopsy a diagnosis of either BOBO or (BOOP) was made.

Open Lung Biopsy Results

The results from the OLB were classified with respect to the information gained. The classifications included (1) new diagnosis: a diagnosis was made that was not suspected before OLB and therapy was changed based on this; (2) confirmed diagnosis: diagnosis on OLB was either clinically suspected or previously pathologically suggested (BAL, TBB, or OLB) and therapy was not affected; (3) suggested diagnosis: diagnosis on OLB was not conclusive and therefore did not change therapy; and (4) nonspecific diagnosis: the OLB findings were nonspecific changes.

The results of OLB and the timing after transplantation are shown in Table 2. A new diagnosis was made in 9 biopsies (24%), a diagnosis was confirmed in 11 biopsies (29%), a second diagnosis was suggested in 2 (5%), and there was no new information in 16 (42%). It is important

Ann Thorac Surg
1995;59:928–32

Table 2. Open Lung Biopsy and Diagnosis Related to Time

	Early		Late		
Result	SLT	DLT	SLT	DLT	Total
New diagnosis	...	1	5	3	9
Confirm	2	...	8	1	11
Suggest	1	...	1	...	2
Nonspecific	4	3	3	6	16
Total	7	4	17	10	38

DLT = double-lung transplantation; SLT = single-lung transplantation.

to note that in early OLBs information that changed therapy (diagnosis made) was obtained in only 1 of 11. However, in the late OLBs a new diagnosis that changed therapy was made in 8 of 27. The diagnoses made in each of these 9 patients are shown in Table 3. The indication categories of patients who had a new diagnosis made by OLB were as follows:

Early	
Perioperative period	1
Late	
Acute or progressive disease	4
Loss of pulmonary function	1
Radiologic compromise	2
Never well	1

Diagnoses that were confirmed by OLB were BO (5), posttransplantation lymphoproliferative disease (2), *Pneumocystis carinii* pneumonia (1), chronic vascular rejection (1), cytomegalovirus infection (1), and acute rejection (1).

Generally, bronchoscopy with TBB was done in an attempt to make a diagnosis and obviate the need for the more invasive OLB. Thus 28 TBBs were done in 26 patients between 3 and 58 days before OLB in DLTs and between 4 and 36 days in SLTs. Discrepant findings (either nonspecific or new diagnosis) between TBB and OLB were found in 20; the discrepant TBB findings were usually acute alveolar injury with mild nonspecific inflammation or nonspecific abnormalities (Fig 1).

In the 9 patients in whom the OLB resulted in a new diagnosis mandating a treatment change, the transbronchial biopsy was done in 6 between 6 and 12 days before OLB. These TBBs showed acute alveolar injury (2), nonspecific changes (2), bronchial ulceration (1), and inadequate specimen (1). The diagnoses after OLB in these 6 patients were BO (2), *Burkholderia cepacia* (1), and BOOP (3). The other 3 patients had two TBBs between 38 and 60 days before OLB.

Table 3. New Diagnosis After Open Lung Biopsy

	SLT	DLT
Bronchiolitis obliterans	2	...
Bronchiolitis obliterans organizing pneumonia	1	3
Lymphoma	1	...
Chronic vascular rejection	1	...
Burkholderia cepacia	...	1
Total	5	4

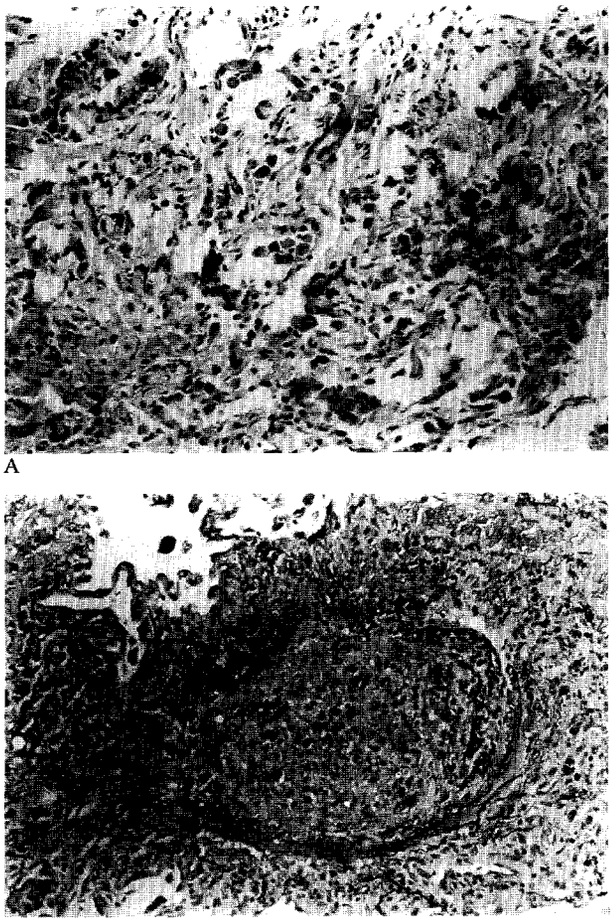

Fig 1. Discrepant biopsy findings in a single-lung transplant with progressive loss in pulmonary function. A transbronchial biopsy 6 months after transplantation showed only nonspecific interstitial inflammation with patchy collections of macrophages within alveoli (A). The light micrograph of the open lung biopsy 1 month later shows a membranous bronchiole occluded by organizing granulation tissue confirming the suspected diagnosis of bronchiolitis obliterans (B). (Hematoxylin and eosin stain and elastic trichrome stain, respectively; original magnification ×63.)

Of the 32 patients who had OLB, 24 have died. Twenty-two of 24 died between 10 and 105 days after OLB. The indications for biopsy in these 22 patients were perioperative period (6), acute or progressive pulmonary disease and clinical findings (12), radiologic compromise without clinical findings (2), and persistent poor graft function (2). Of these 22 recipients 4 had OLB twice for the same indication. Of the 26 biopsies a new diagnosis was made in 5, a diagnosis was confirmed in 7, a diagnosis was suggested in 2, and 12 had nonspecific pathology. The new diagnoses were BO (2), BOOP (1),

BOOP and *Burkholderia cepacia* (1), and BO and CVR (1). The diagnoses that were confirmed were BO (3), *P carinii* pneumonia (1), lymphoma (1), chronic vascular rejection (1)—a second biopsy in the patient in whom chronic vascular rejection was diagnosed on the first OLB—and cytomegalovirus (1). Suggested diagnoses were herpes pneumonia (1) and lymphoma (1)—later confirmed by a second biopsy. Of the 12 biopsies with nonspecific diagnosis (10 patients) autopsy diagnoses were infections (6), BO (3), and PTLD (1). Of these 22 deaths, 6 were in patients in the early group and 16 in the late group of biopsies.

Twenty-one of the 24 patients who died underwent autopsy, and a new diagnosis was found in 3: disseminated *Aspergillus* in 2 and systemic candidiasis in 1. Of the patients with *Aspergillus* infection (both SLTs), 1 had a nondiagnostic OLB 20 days before death and the other had a BOOP diagnosis on OLB 3½ months premortem. The patient with systemic candidiasis was a SLT patient with OLB confirming *P carinii* pneumonia 20 days before death. All 3 patients were in the group with acute or progressive pulmonary disease and clinical findings. These patients died 11, 20, and 105 days after OLB. Because of the interval between OLB and death, it is likely that the infections found at autopsy were not present at the time of OLB and may represent subsequent complications of the patients' underlying problems.

Of the 38 OLBs, 12 were performed during the first 6 years of our lung transplantation experience (1983–1989) when a total of 49 patients underwent lung transplantation. The remaining 26 OLBs have been performed since 1990, during which a total of 95 patients received lung grafts. Thus, approximately the same proportion of OLBs were done in the early and mature stages of our lung transplant program even though the lung transplant team members had gained considerable experience in dealing with complications of lung transplantation.

Complications after OLB occurred in 4 patients (12%). One patient had a bronchopleural fistula requiring prolonged drainage; he died 20 days after OLB. Two other patients also had a prolonged air leak with resulting empyema requiring Claggett procedures. In the fourth patient a hemothorax developed requiring reexploration after OLB. A diagnosis of BOOP was made by OLB in 3 of the 4 patients experiencing these complications. Of these 4 patients, only 1 was early after transplantation (1 month) and the other 3 were 53, 10, and 5 months after transplantation.

Comment

Lung transplantation has become routine and successful with a current 2-year survival of about 62% [6]. However, long-term survivors continue to be plagued by a high rate of complications, especially infections and chronic rejection.

In spite of the routine use of bronchoscopy with TBB and BAL for surveillance monitoring and as a relatively sensitive and specific way to make diagnoses when specific clinical situations develop, it sometimes is necessary to turn to more invasive procedures.

The Pittsburgh lung transplant group [7] have reported that when OLB was performed after TBB on ten occasions in which the clinical situation was uncertain, new information was obtained in only three instances. They did not note the relevant diagnoses nor the posttransplantation timing of the OLB. Magee and associates [8], in a more recent publication from the same group, reported five OLBs performed through thoracoscopy in 5 lung transplant recipients after TBB had failed to establish a diagnosis. In their hands this approach was effective with little morbidity when TBB was contraindicated or nondiagnostic and the procedure could be done electively.

Our experience with OLB in this population is instructive. Open lung biopsy was of little value in the perioperative period, but yielded useful information that resulted in changed treatment strategy in approximately 30% of patients when performed more than 45 days after transplantation. The indication for OLB did not accurately predict whether useful information would be gained, although more new diagnoses came from the group with acute or progressive pulmonary disease and clinical findings. Also it is noteworthy that discrepant findings were common between OLB and TBB material, with TBB material often yielding nonspecific and, therefore, not useful information in many patients who went on to OLB. This may reflect inadequate representation, patchiness of the disease process with sampling error, or the nonspecific nature of the process when seen in very small samples (as, for example, in BOOP).

It also is worth noting that although new diagnoses were made in only nine of 38 OLBs, in 11 more a suspected diagnosis was confirmed. This may be useful information for the treating transplant team because, although it may not result in a better outcome, it confirms the use of on-going therapy and may prevent the use of "shotgun" expensive and nonindicated presumptive therapy because of uncertainty about diagnosis.

Interestingly, despite considerable experience with pulmonary complications and more clinical confidence in dealing with these problems, the rate of OLB did not change between the early years of the program and the more recent years.

The complication rate from OLB was not excessive (12%), but the morbidity from these complications was significant. Of these 4 patients 3 had OLB 53, 10, and 5 months after transplantation for acute or progressive pulmonary disease and only 1 during the perioperative period with mechanical ventilation. It is interesting that half of the complications occurred in patients who had diffuse infiltrates diagnosed as BOOP on the OLB.

Despite the availability of experienced lung transplant clinicians for assessment of complications in transplant recipients, we have found that a number of occasions arise in which it is not possible clinically, with laboratory tests, or even with bronchoscopy to diagnose pulmonary processes in this complicated group of patients. Thus, there is a continuing need for OLB diagnoses, which we have found will add useful information and change

management in about a third of patients more than 45 days after transplantation. We recommend that long-term survivors with ongoing undiagnosed respiratory deterioration or unexplained new chest radiographic findings undergo OLB if less invasive procedures are nondiagnostic.

References

1. Higenbottam T, Stewart S, Penketh A, Wallwork J. Transbronchial lung biopsy for the diagnosis of rejection in heart-lung transplant patients. Transplantation 1988;46:532–9.
2. Trulock E, Ettinger N, Brunt E, Pasque M, Kaiser L, Cooper J. The role of transbronchial lung biopsy in the treatment of lung transplant recipients. An analysis of 200 consecutive procedures. Chest 1992;102:1049–54.
3. Tazelaar H, Nilsson F, Rinaldi M, Murtaugh P, McDougall J, McGregor C. The sensitivity of transbronchial biopsy for the diagnosis of acute lung rejection. J Thorac Cardiovasc Surg 1993;105:674–8.
4. De Hoyos A, Chamberlain D, Schvartzman R, et al. Prospective assessment of standardized pathologic grading system for acute rejection in lung transplantation. Chest 1993;103: 1813–8.
5. Chaparro C, Maurer J, Chamberlain D, et al. Causes of death in lung transplant patients. J Heart Lung Transplant 1994;13: 758–66.
6. St. Louis International Lung Transplant Registry. April 1994 Report.
7. Paradis I, Duncan S, Dauber J, Yousem S, Hardesty R, Griffith B. Distinguishing between infection, rejection, and the adult respiratory distress syndrome after human lung transplantation. J Heart Lung Transplant 1992:11:S232–6.
8. Magee MJ, Fitzgibbon L, Durham S, et al. Thoracoscopy in the evaluation and treatment of lung transplant recipients. J Heart Lung Transplant 1993;12(80 Suppl):A63.

Notice From the American Board of Thoracic Surgery

The American Board of Thoracic Surgery began its recertification process in 1984. Diplomates interested in participating in this examination should maintain a documented list of the operations they performed during the year prior to application of recertification. This practice review should consist of 1 year's consecutive major operative experiences. (If more than 100 cases occur in 1 year, only 100 need to be listed.) They should also keep a record of their attendance at approved postgraduate medical education activities for the 2 years prior to application. A minimum of 100 hours of approved CME activity is required.

In place of a cognitive examination, candidates for recertification will be required to complete both the general thoracic and cardiac portions of the SESATS V syllabus (Self-Education/Self-Assessment in Thoracic Surgery). It is not necessary for candidates to purchase SESATS V booklets prior to applying for recertification. SESATS V booklets will be forwarded to candidates after their applications have been accepted.

Diplomates whose 10-year certificates will expire in 1997 may begin the recertification process in 1995. This new certificate will be dated 10 years from the time of expiration of the original certificate. Recertification is also open to any diplomate with an unlimited certificate and will in no way affect the validity of the original certificate.

The deadline for submission of applications is May 1, 1995. A recertification brochure outlining the rules and requirements for recertification in thoracic surgery is available upon request from the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.