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Native lung complications after single lung transplantation for emphysema

Received: 2 July 1996
Received after revision: 15 October 1996
Accepted: 28 October 1996

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Abstract We reviewed the impact of the presence of the native diseased contralateral lung on the outcome after single lung transplantation for emphysema. Twenty consecutive recipients of single lung transplants for emphysema were reviewed for complications related to the native lung. Five patients (25%) suffered major complications arising in the native lung and resulting in serious morbidity and mortality. The timing of onset varied from 1 day to 43 months after transplantation. We conclude that the susceptibility of the native lung to complications such as those described in this report is an additional fact to be considered in choosing the ideal transplant procedure for patients with obstructive lung disease.

Key words Emphysema, single lung transplantation, native lung · Lung transplantation, native lung, emphysema · Native lung, single lung transplantation, emphysema

Introduction

Suitably selected patients with end-stage emphysema can be treated by either single or double lung transplantation [6, 12]. The ability to transplant two lungs from a single donor into two separate recipients is a powerful factor in promoting single lung transplantation as the procedure of choice for this indication. Single lung transplantation is, therefore, the operation of choice in our institution for patients with end-stage emphysema, except for those patients with a major, recurrent, bronchitic component who are offered double lung transplantation. The contralateral diseased native lung, however, remains a potential source of complications that may impair both early and late outcomes [5]. We describe complications arising in the native lung that result

in significant morbidity and mortality following single lung transplantation for emphysema.

Methods

This report constitutes our experience with 20 consecutive single lung transplants for emphysema (13 for alpha-1 antitrypsin deficiency) from June 1990 to September 1995. Seven right lungs and 13 left lungs were transplanted in 8 males and 12 females, aged 40–62 (mean 52.4) years. Total follow-up was 14677 patient/days (range 3–2065 days). One other emphysema patient who had recurrent bronchitis and pneumonitis underwent double lung transplantation; this patient is alive 3.5 years after surgery and is not included in this report. None of the patients included in this series had any evidence of bronchial or pulmonary infection at the time of transplantation.

Table 1 Complications of the native lung and time of onset

Patient	Complications	Onset
1	Hyperinflation	1 day
2 ^a	<i>Pseudomonas</i> pneumonitis	1 month
3	<i>Aspergillus</i> infection	8 months
4	<i>Aspergillus</i> infection	16 months
5	Squamous cell carcinoma	43 months

^aThis patient also developed B-cell lymphoma in the native lung 6 months after transplantation

Surgical techniques have been described previously [11]. Immunosuppression included:

1. Methylprednisolone: 500 mg intravenously (i.v.) after organ perfusion, 125 mg i.v. every 8 h for 24 h
2. Azathioprine: 4 mg/kg loading dose, 1–2.5 mg/kg/day⁻¹ to maintain the white blood cell count at 4000–6000/ μ l
3. OKT3: 5 mg i.v. intraoperatively, 30 min after methylprednisolone, and then 2.5 mg i.v./qd \times 12 doses
4. Cyclosporin (CyA): started in the 2nd postoperative week and adjusted to maintain serum trough levels (CyA and metabolites) at 200–300 ng/ml for 6 weeks and at 75–150 ng/ml thereafter
5. Prednisone: 1 mg/kg/day⁻¹ beginning on day 15, 0.3 mg/kg/day⁻¹ from the 1st to 6th months, and 0.2 mg/kg/day⁻¹ thereafter.

All in-hospital and outpatient records were reviewed. All complications related specifically to the native lung that required treatment or that led to significant morbidity or mortality were documented.

Results

The 1-year Kaplan-Meier actuarial survival rate for all patients receiving single lung transplantation for emphysema at this institution is 81 % \pm 8.6 % (as of 15 September 1996).

Complications related specifically to the native lung occurred in five patients (25 % of recipients). The nature of these complications and their time of onset, extending from early postoperatively to beyond 3 years after transplantation, are given in Table 1. There was no significant difference between these 5 patients and the remaining 15 patients in terms of the incidence of rejection or infection. In addition, total doses of immunosuppressive agents were not significantly different between the two groups. Brief case reports of the 5 patients with complications follow.

Case 1

A 48-year-old woman with emphysema (non- α 1-antitrypsin deficiency) underwent left single lung transplantation. After extubation on the 1st postoperative day, hyperinflation of the native lung was evident, shifting the mediastinum to the left and causing atelectasis of the lower lobe of the transplanted lung. Bronchoscopy, bronchoalveolar lavage (BAL), and transbronchial biopsy (TBB) showed no abnormality in the transplanted lung. Respiratory parameters showed a normally compliant transplanted lung and a highly compliant native lung with air trapping.

After several attempts at extubation had failed, a native lung middle and lower lobectomy was done. After surgery the patient had a prolonged air leak that required chest tube drains in place for 30 days. This patient was recovering and ambulating when she suddenly died on postoperative day (POD) 70 of ventricular fibrillation. Autopsy showed a large, recent, anterior myocardial infarction secondary to spontaneous dissection of the left anterior descending coronary artery. The transplanted lung showed no evidence of rejection or infection.

Case 2

A 59-year-old man with emphysema (α 1-antitrypsin deficiency) underwent left single lung transplantation. When a donor lung became available, serology revealed cytomegalovirus (CMV) and Epstein-Barr virus (EBV) mismatch (donor positive, recipient negative). TBB was performed twice in this patient, showing both times grade 0 rejection. One month after transplantation, the patient developed native upper lobe pneumonia. *Pseudomonas aeruginosa* was detected by BAL. Six months after transplantation, the patient developed a malignant B-cell lymphoma in the native lung (diagnosed by TBB).

Despite aggressive chemotherapy, this patient died 9 months after transplantation of respiratory failure. Autopsy showed invasive aspergillosis in both lungs and three large lymphomatous nodules in the right (native) lower lobe. No signs of rejection or obliterative bronchiolitis (OB) were found.

Case 3

A 43-year-old man with emphysema (α 1-antitrypsin deficiency) underwent right single lung transplantation. This patient, who was a CMV mismatch, developed multiple episodes of CMV pneumonitis and viremia. TBB, performed twice, showed no signs of rejection. Investigation of a new native lung infiltrate at 8 months after transplantation by BAL and TBB showed invasive pulmonary aspergillosis. He was treated with amphotericin B for 1 week and then, due to severe renal dysfunction, was switched to long-term oral therapy with itraconazole.

This patient died 15 months after his transplantation of acute hemorrhagic pancreatitis in a setting of CMV viremia. The native lung at autopsy was free of both CMV and *Aspergillus* infection. The graft was free of rejection and OB.

Case 4

A 57-year-old woman with emphysema (non- α 1-antitrypsin deficiency) underwent right single lung transplantation. TBB performed 2 and 4 months after transplantation showed grade 2A rejection; the first episode was treated with an oral steroid taper, the second with pulsed i.v. methylprednisolone for 3 days. Sixteen months after transplantation, the patient was admitted for shortness of breath and deterioration in pulmonary function tests. TBB showed OB. During this hospital admission, the patient developed a rapidly growing mass in her native upper lobe that was shown by a needle aspirate to be an *Aspergillus* abscess, from which she died on POD 522. Autopsy confirmed obstructive bronchiolitis in her transplanted lung and fungal infection confined to her native lung.

Case 5

A 64-year-old woman underwent left single lung transplantation for emphysema (α 1-antitrypsin deficiency). TBB was performed three

times during the 1st year and was always negative for rejection. She developed hemoptysis 3.5 years later. A chest CT showed a 3 × 3.5-cm mass in her right upper lobe that was identified as squamous cell carcinoma. The patient underwent right upper and middle lobectomy of her native lung and developed a persistent air leak that ultimately required the insertion of a chest tube connected to a Heimlich valve. She was discharged from the hospital with the Heimlich valve in place. She continued to improve, and 45 days later the chest tube was removed without further complications. This patient died 5 years after transplantation of multiorgan failure in a setting of severe myopathy, generalized cachexia, and disseminated angioinvasive aspergillosis. Mild OB was also present in the graft.

Discussion

The ideal lung transplant procedure (single or bilateral) for end-stage emphysema is uncertain [1, 3, 4, 11]. Single lung transplantation offers the opportunity to transplant two lung recipients from one donor. The surgical procedure is shorter and easier. The St. Louis International Lung Transplant Registry reports similar 3-year survival rates after single lung transplantation and double lung transplantation for emphysema/chronic obstructive pulmonary disease [12], while the Registry of the International Society of Heart and Lung Transplantation reports better survival curves after single lung transplantation [6].

The presence of a transplanted lung in parallel with a native emphysematous lung does not per se cause a life-threatening ventilation/perfusion mismatch as long as the mechanical characteristics of the graft are not impaired by complications in the pulmonary graft (e. g., reperfusion injury, rejection, infection) [7, 8, 13, 14]. The

native lung can provide a “backup” margin of safety in the case of severe perioperative graft dysfunction or severe rejection [7, 9, 10, 14].

Disease in the native emphysematous lung, however, presents a potential for complications of its own due to a predisposition to infections secondary to decreased mucociliary clearance, altered sputum characteristics and, at times, chronic bacterial colonization [2]. Interestingly, in our series, contralateral spread of infection from the native lung was not documented. A propensity for the development of lung cancer in recipients with long smoking histories is also present. The incidence and nature of such complications may vary according to the underlying lung pathology [5]. In patients with emphysema in this study, these complications resulted in serious morbidity and increased mortality. Findings from this study emphasize the need to continue improving the long-term management of single lung transplant recipients.

Routine prophylactic therapy with itraconazole (monitored by serum levels) has been introduced in all lung transplant patients in our program. This has resulted anecdotally in a reduction in the incidence of *Aspergillus* infections. All patients are also maintained on lifelong *Pneumocystis* prophylaxis with sulfamethoxazole-trimethoprim. In recipients who are CMV-positive, prophylactic therapy with ganciclovir (i. v. and/or oral) is given for 3 months after transplantation.

The susceptibility of the native lung to complications such as those described in this report is an additional factor to be considered in choosing the ideal transplant procedure for patients with obstructive lung disease. Good early outcome has been obtained, but satisfactory late survival continues to be a challenge [10, 12].

References

- Bates DV (1970) The other lung. *N Engl J Med* 282: 277-279
- Colquhoun IW, Gascoigne AD, Gould K, Corris PA, Dark JH (1991) Native pulmonary sepsis after single-lung transplantation. *Transplantation* 52: 931-933
- Cooper JD, Patterson GA, Grossman R, et al (1989) Double-lung transplant for advanced chronic obstructive lung disease. *Am Rev Respir Dis* 139: 303-307
- Cooper JD, Patterson GA, Trulock EP, Washington University Lung Transplant Group (1994) Results of single and bilateral lung transplantation in 131 consecutive recipients. *J Thorac Cardiovasc Surg* 107: 460-471
- Frost AE, Keller CA, Noon GP, Short HD, Cagle PT, and the Multiorgan Transplant Group (1995) Outcome of the native lung after single lung transplant. *Chest* 107: 981-984
- Hosenpud JD, Novick RJ, Breen TJ, et al (1994) The Registry of the International Society for Heart and Lung Transplantation: eleventh official report - 1994. *J Heart Lung Transplant* 13: 561-570
- Kaiser LR, Cooper JD, Trulock EP, et al (1991) The evolution of single lung transplantation for emphysema. *J Thorac Cardiovasc Surg* 102: 333-341
- Koerner SK, Veith FJ (1974) Ventilation-perfusion relationship between transplanted and emphysematous lungs. *Vasc Surg* 8: 283-297
- Low DE, Trulock EP, Kaiser LR, et al (1992) Morbidity, mortality and early results of single versus bilateral lung transplantation for emphysema. *J Thorac Cardiovasc Surg* 103: 1119-1126
- Marinelli WA, Hertz MI, Shumway SJ, et al (1992) Single lung transplantation for severe emphysema. *J Heart Lung Transplant* 11: 577-583
- McGregor CGA, Daly RC, Peters SG, et al (1994) Evolving strategies in lung transplantation for emphysema. *Ann Thorac Surg* 57: 1513-1521
- St. Louis International Lung Transplant Registry (1995) April report
- Veith FJ, Koerner SK, Siegelman SS, et al (1973) Single lung transplantation in experimental and human emphysema. *Ann Surg* 178: 463-477
- Zannini P, Baisi A, Melloni G, et al (1992) Single lung transplantation for emphysema. Lessons learned on the field. *Int Surg* 77: 28-36