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Late postoperative pleural effusion following lung transplantation: characteristics and clinical implications

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Abstract

Objective: Pleural effusions are extremely common in the early postoperative period after lung transplantation (LTX). It occurs in all transplant recipients, and like pleural fluid following other cardiothoracic surgery is bloody, exudative and neutrophil predominant. There was no information, however, on the characteristics of the late (14–45 days) postoperative pleural fluid after LTX. The purpose of this study was to describe the characteristics and the clinical implications of late postoperative pleural effusion after LTX. **Methods**: Thirty-five patients underwent TX between May 1997 and May 2001. Seven patients (20%) developed late postoperative pleural effusion. Thoracentesis were performed in these patients and the white blood cell counts, cell differential as well as biochemical parameters were determined. **Results**: The median time for late pleural effusion appearance was 23 days (range, 14–34 days) after TX. The pleural effusions were medium in size (700 ml, range, 100–1300), exudative in all the patients and had lymphocyte predominance. No evidence of fluid recurrence or clinical deterioration was noted in these patients. **Conclusion**: Late-onset exudative lymphocytic pleural effusion after LTX is not uncommon. When there is no evidence of rejection or infection, it usually has a benign, favorable outcome.

Keywords: Pleural effusion; Transplantation; Rejection

1. Introduction

Lung transplantation (LTX) has become a feasible therapeutic option for selected patients with end-stage pulmonary disease [1–3]. Refinements in the selection of candidates, operative technique and long-term care of recipients have resulted in improved outcome and a dramatic decrease in post-TX complications. Nevertheless, pleural effusions are extremely common in the early (within 9 days) postoperative period [4,5]. Chiles et al. [4] reported a 100% incidence in ten patients after heart–lung TX. These effusions are usually bloody, exudative, neutrophil predominant and usually small to moderate in size. They tend to resolve spontaneously within 9 days of TX [5].

There is only one report on late (more than 14 days) pleural effusions following LTX [7]. Herridge et al. [6] reviewed the pleural complications of unilateral and bilateral LTX. They reported that 14 of 91 (15%) double-lung transplant recipients had pleural effusions, whereas none of the 53 single-lung transplant recipients did so. The effusions consisted of empyemas in seven patients, parapneumonic effusions that resolved spontaneously in four, hemothorax in two and chylothorax in one. There was no information, however, on the characteristics and the clinical implication of late postoperative pleural fluid after LTX. In the present study, we report on our experience with late postoperative pleural effusion, which occurred following LTX in seven patients.

2. Patients and methods

Between May 1997 and May 2001, 35 patients in our department underwent heart–lung ($n = 4$), double-lung ($n = 3$) or single-lung ($n = 28$) TX. Pleural effusion

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Table 1
Characteristics of transplant recipients[a]

Patient no.	Sex/age (years)	Lung disease	Procedure
1	M/52	A1AT	SLT/R
2	M/53	Emphysema	SLT/L
3	M/25	PPH	HLT
4	F/58	Emphysema	SLT/L
5	F/55	IPF	SLT/R
6	F/49	IPF	SLT/R
7	M/49	IPF	DLT

[a] A1AT, alpha one antitrypsin; PPH, primary pulmonary fibrosis; IPF, idiopathic pulmonary fibrosis; SLT, single-lung transplant; HLT, heart–lung transplant; DLT, double-lung transplant.

developed in ten of them (29%) within the first 3 months following LTX, all of whom underwent thoracentesis. Immunosuppression regimen included combination of tacrolimus (FK-506), mycophenolate mofetil (MMF) and corticosteroids (CS) in all the recipients The total pleural fluid output from the chest tube was recorded, as were the pleural fluid red and white blood cell counts, the cell differentiation count and the lactate dehydrogenase (LDH), total protein, amylase, total cholesterol, triglyceride and glucose levels. The cause of the pleural effusions was evaluated by pleural fluid staining and cultures for bacteria, mycobacteria and fungi. Pulmonary function tests, bronchoscopy with bronchoalveolar lavage and transbronchial biopsy were performed as well. Postoperative pleural effusion defined as pleural effusion that occurred after LTX without other possible causes like parapneumonic effusion, empyema and pleural effusion secondary to acute rejection. None of the patients had low plasma albumin level, diuretic treatment.

3. Results

Ten recipients (29%) developed late pleural effusions after LTX during the 3 months following TX. Three patients were excluded from the study: two with parapneumonic effusion and one with acute rejection. Patient characteristics of the seven affected lung-transplant patients with late postoperative are outlined in Table 1. Three patients had emphysema, three, idiopathic pulmonary fibrosis and one primary pulmonary hypertension. Five underwent single-LTX, three of them on the right side. One underwent heart–lung TX and one double-LTX. The pleural fluid analyses of the lung transplant recipients are shown in Tables 2 and 3. The median time from TX to the appearance of the pleural effusion was 23 days (range, 14–34 days).

All the pleural effusions were of medium size, with a median fluid volume of 700 ml (range, 100–1300 ml). Chest tube withdrawal was 1–2 days after insertion in all the patients. They were exudative in all patients, and all had lymphocyte predominance. In one patient, eosinophils were noted and in two patients, a bloody fluid was observed.

Two patients had very high levels of LDH, without apparent significant clinical correlation. No evidence of fluid recurrence or clinical deterioration was noted.

4. Discussion

There are several explanations for the accumulation of pleural fluid in the early postoperative period [8,9]. Siegelman et al. [9] attributed this finding to the increased permeability of the alveolar capillaries in the first few days after TX due to allograft ischemia, denervation and subsequent reperfusion. Furthermore, allograft lung lymphatics are severed during TX so that lymphatic flow is severely disrupted. According to two animal studies, the allograft lymphatics are reconstituted and become functional 2 weeks after TX [10,11]. Most probably, all these mechanisms attributed also to the late onset pleural effusion in the first month following the TX.

Pleural effusions are associated with acute lung rejection, an event that occurs at least once in almost all lung-transplant recipients [12]. Bergin et al. [13] assessed the correlation between chest radiograph and lung biopsy results in 16 heart–lung TX patients. They found that the combination of septal lines and new or increasing pleural effusions was predictive of acute lung rejection with sensitivity of 68%, specificity of 90% and overall accuracy of 83%. We excluded in our study, however, the pleural effusion secondary to lung rejection. Judson et al. [8,14] conducted studies in the course and characteristics of early pleural effusion in single-lung-transplant recipients. They

Table 2
Pleural fluid characteristics following LTX ($n = 7$)[a]

Patient no.	Days since Tx	Total fluid (ml)	Appearance	WBC/mm^3	Neutrophils (%)	Lymphocytes (%)	Eosinophils (%)
1	23	600	Y	1310	3	92	0.7
2	14	900	B	4000	29	62	0.1
3	34	1200	Y	7750	0.7	94	1.4
4	22	1300	Y	5540	18.6	77.6	0.4
5	14	700	B	2450	7	78	0.2
6	30	200	Y	1360	13	75	0.5
7	18	100	Y	2800	19	54	13

[a] Tx, transplantation; Y, yellowish; B, bloody.

Table 3
Pleural fluid biochemical parameters characteristics following LTX ($n = 7$)

Patient no.	Total protein (g/dl), serum/pleural	Cholesterol (mg/dl)	Triglyceride (mg/dl)	Amylase (IU/l)[a]	LDH (IU/l)[b], serum/pleural	Glucose (mg/dl)
1	5.6/3.6	197	ND[c]	62	377/352	88
2	5.7/5.0	52	24	42	536/3242	27
3	6.5/3.8	43	15	22	340/412	71
4	5.6/3.3	68	38	25	322/707	109
5	6.3/2.9	195	ND	29	493/788	80
6	6.3/3.9	128	36	18	503/367	85
7	4.9/4.6	30	15	16	560/977	34

[a] Upper limit of plasma normal levels in our laboratory is 220 IU/l.
[b] Upper limit of plasma normal levels in our laboratory is 480 IU/l.
[c] ND, not done.

found that the pleural effusion immediately after TX tends to be bloody, exudate, neutrophil predominant and continuing for up to 9 days. They concluded that early postoperative pleural effusion need not be analyzed if the fluid output is steadily decreasing and the clinical course is appropriate. The same authors also reported on one lung-transplant recipient with late-onset pleural effusion in which they concluded that the differential diagnosis of exudative, lymphocyte-predominant lung fluid should include acute lung rejection.

Besides this case report, few data are available regarding late postoperative pleural effusion that occurred more than 2 weeks after LTX. Our analysis in seven patients demonstrated that like early postoperative pleural effusion, late postoperative pleural effusion is a common complication. Like early postoperative pleural effusion, it is exudative but in contrast to the early pleural fluid, it is lymphocyte-predominant, except when there is clinical evidence of infection. The effusions are moderate in size and usually do not recur after thoracentesis. Acute rejection is the most acceptable diagnosis of exudative pleural effusion in lung recipients after exclusion of such systemic diseases as pneumonia, tuberculosis and lymphoma [15]. In our patients, the benign course without steroid treatment and the resolution of symptoms without recurrence of the pleural fluid made the diagnosis of rejection less likely.

We conclude that late postoperative exudative lymphocyte-predominant pleural effusion after LTX in the absence of clinical evidence of rejection or infection is a common complication and does not usually recur after thoracentesis.

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