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Lung transplantation in patients with scleroderma: case series, review of the literature, and criteria for transplantation

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Abstract: Backgrounds: The use of lung transplantation (LTX) to treat respiratory failure because of scleroderma is controversial. We present our experience, review the current literature, and suggest specific criteria for LTX in scleroderma. Of the 174 patients who underwent LTX at our center, seven (4%) had scleroderma-associated respiratory failure.
Patients and methods: A MEDLINE search of the English literature was performed for studies of LTX in patients with scleroderma between 1986 and 2006. A Kaplan–Meier survival curve was calculated over the time of the studies.
Results: The MEDLINE search yielded one large review and four small case series. The small case series were included in the review. The review and our series yield a total of 54 patients. Mean patient age was 47.1 yr; 59.3% were female. Pre-operative lung data were available for 24 patients: 22 (92%) had pulmonary fibrosis and 17 (71%) had pulmonary hypertension. Most patients (69%) underwent single-lung transplantation. Mean forced expiratory volume at one s after LTX was 67% (range 56–87%). There was no difference in infection and rejection rates between the patients with scleroderma and other LTX recipients. The two- and five-yr survival rates were 72% and 55%, respectively.
Conclusions: LTX is a valid option in well-selected patients with scleroderma and pulmonary fibrosis, yielding good pulmonary function and acceptable morbidity and mortality.

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Key words: lung transplantation – pulmonary fibrosis – pulmonary hypertension – reperfusion injury – scleroderma

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The past decade has witnessed a steady increase in the number of patients undergoing lung transplantation (LTX). Nevertheless, patients with systemic collagen disease are often excluded from the candidate list because of concerns about the short- and long-term outcomes especially patients survival (1).

Scleroderma is a collagen vascular disease with varying degrees of skin and internal organ involvement. The organs most commonly affected are the kidney, gastrointestinal tract, lung, and heart (2). Use of angiotensin-converting enzyme inhibitors has greatly reduced the renal complications, making lung disease the leading cause of morbidity and mortality in patients with scleroderma (3). The two major presentations of scleroderma-associated lung disease are pulmonary fibrosis and pulmonary hypertension (HTN) (4).

Owing to the small number of lung transplants that have been performed in patients with scleroderma, there are only a few published reports on the long-term outcome in this setting (1, 5–7). The aims of this study were to present our experience with LTX in seven patients with scleroderma, to review the current literature concerning lung transplants and scleroderma, and to suggest specific criteria for LTX in patients with scleroderma.

Patients and methods

Case series

Between January 1997 and September 2006, 174 lung and heart-lung transplantations were performed at Rabin Medical Center, Beilinson Campus, Israel. All received an immunosuppressive regimen of tacrolimus (FK506), mycophenolate mofetil, and prednisone, in addition to prophylaxis with itraconazole, trimethoprim-sulfamethoxazole, ganciclovir, and oral nystatin. Follow-up included complete blood counts, blood chemistries (including renal function), drug levels, chest radiographs, pulmonary function tests in all cases. Surveillance bronchoscopies were done three, seven and 30 days after LTX and in every case when clinically needed.

In all our lung transplants, mean pulmonary arterial pressure (PAP) was measured by right heart catheterization pre- and post-transplantation. All the patients underwent routine perfusion-ventilation scan before LTX and three, six, 12 months after LTX, and then, every year after the transplantation. Primary graft dysfunction grade was calculated according to the International Society for Heart and Lung Transplantation (ISHLT) working group (8).

Seven cases (4%) underwent LTX because of scleroderma. All seven patients were treated with corticosteroids and cyclophosphamide for their lung fibrosis prior to the LTX. Five patients developed the lung disease one to two yr after their systemic disease. Two patients developed the fibrosis after six yr from the systemic disease. The files of these patients were reviewed for pre- and post-operative pulmonary complications, presence of reflux, degree of skin involvement, renal function, operative course, immunosuppression and prophylaxis regimens, and findings on follow-up.

The diagnosis of gastroesophageal reflux in all patients was based on suggestive symptoms (heartburn and aspiration) and esophagogastroscopy with signs of esophagitis. The Ethics Committee of Rabin Medical Center approved the study.

Review of the literature

A MEDLINE search of the English literature was performed for years between 1986 and 2006 using the key words ''scleroderma,'' ''systemic sclerosis,'' ''lung transplantation,'' ''pulmonary fibrosis,'' and ''pulmonary hypertension,'' alone or in combination. Data on the patients with scleroderma who underwent LTX were collected. A Kaplan–Meier survival curve was calculated over the time of the studies, including our case series. On the basis of the findings in the literature and our own experience, we formulated criteria for LTX in patients with scleroderma.

Results

Case series

Clinical characteristics. The clinical characteristics of our study patients are shown in Table 1. The group included five female and two male patients of median age 52 yr (range 47–53 yr). All had the diffuse form of pulmonary fibrosis preoperatively and were positive for anti-Scl-70 antibodies. All were treated with steroids and immunosuppression (five with cyclophosphamide and two with methotrexate). All but one patient also had pulmonary HTN, with a median PAP of 48 mmHg (range 42–70 mmHg), and all but one had gastrointestinal reflux, ranging from mild without aspiration in four patients to moderate with intermittent aspiration (but not aspiration pneumonia) in two. Two patients had serious skin involvement including Raynaud's phenomenon with finger autoamputation. Renal function was normal in all patients. In all cases, the pulmonary complication occurred in the first three yr of their non-pulmonary complications.

Table 1. Clinical characteristics of patients with scleroderma in our institute undergoing lung transplantation (n = 7)

Patient no.	Sex/age (yr)	Time to LTX (months)	Type of LTX	Reflux	Skin involvement	Follow-up (months)	PAP (mmHg)		BUN (mg/dL)		Creatinine (mg/dL)	
							Pre-LTX	Post-LTX	Pre-LTX	Post-LTX	Pre-LTX	Post-LTX
1	F/52	48	SLT-Rt	Mild	–	50	64	32	39	31	0.9	0.9
2	M/54	9	SLT-Rt	Moderate	+	38	48	36	44	23	1.6	1.2
3	F/51	14	SLT-Rt	Mild	–	–	42	–	20	–	0.7	–
4	M/52	23	SLT-Lt	Moderate	–	5	70	38	45	29	1.2	0.7
5	F/53	36	SLT-Lt	Mild	+	8	45	38	32	41	0.8	1.2
6	F/53	60	SLT-Rt	Mild	–	6	29	15	69	39	0.7	0.8
7	F/47	60	SLT-Rt	–	–	10	50	28	41	47	0.6	0.6

BUN, blood urea nitrogen; LTX, lung transplantation; PAP, pulmonary arterial pressure; SLT, single-lung transplantation.

All patients underwent single-lung transplantation (SLT) (five right side, two left side). The median time to transplantation from diagnosis of the pulmonary complications was 23 months (range 9–60), and the median duration of post-operative follow-up was 12 months (range 9–50 months).

After LTX, median PAP dropped to 36 mmHg (range 15–30 mmHg) (Table 1). All patients had some degree of reperfusion injury perioperatively, resulting in pulmonary edema, which resolved in six patients within two to three d but was fatal in one (patient no. 3). The PGD grade of the patients was 1 in three patients, 2 in an other three patients and 3 in the patients who died (Table 1).

Pulmonary lung functions. Lung functions before and after LTX are shown in Table 2. Improvement was noted in median total lung capacity, which increased from 56% (range 49–94%) to 72% (range 47–117%), median diffusion capacity of carbon dioxide, which increased from 24% (range 16–46%) to 46% (range 24–68%), and median oxygen saturation (Sat O_2) at rest, which increased from 87% (range 86–97%) to 98% (range 97–99%). The improvement in Sat O_2 was noted especially after exercise, with an increase from a median of 82% (range 81–94%) before LTX to 96% (range 94–99%) after. A similar improvement was observed in perfusion to the transplanted lung, which increased from a median of 50% (range 33–60%) to 68% (range 63–85%).

Following a median follow-up of 12 months, the survival of the patients with scleroderma (88%) was similar to the survival of the non-scleroderma lung-transplant recipients at our center (84%). Twelve episodes of acute rejections were observed during the follow-up, all treated with intravenous methylprednisolone 1 g/d for three d, followed by tapering down. Ten episodes of infections occurred, nine of them were bacterial infections (all pneumonia) that responded to broad spectrum antibiotics, and one was a viral infection (herpes zoster). All the infections occurred in the transplant lungs. In addition, the infection and rejection rates in the study population were similar to the non-scleroderma lung-transplant recipients. The three-yr survival rate in our patients with scleroderma was 73%.

Review of the literature

Our MEDLINE search and our case series yielded five studies, one review and four case series. All data from the four case series in the literature (1, 5–7, 9) were included in the large review. The data from the review as well as from our case series (54 patients) are summarized in Table 3. The review included short- and long-term morbidity and mortality in 47 patients treated at 23 U.S. centers between 1987 and 2004 (9).

Mean age of the 54 reported patients was 47.1 yr; 59.3% were female. Preoperative lung data were available for 24 patients: 22 (92%) had pulmonary fibrosis and 17 (71%) had pulmonary HTN. All the patients with pulmonary HTN also had pulmonary fibrosis. Thirty-four patients (63%) underwent SLT and 20 patients (37%) double-lung transplantation (DLT); the mean duration of post-operative follow-up was 32.3 months (range 8–60).

All the studies but one (9) reported the pulmonary function results following LTX. Mean forced expiratory volume at one s was 67% (range 56–87%). None of the three studies that compared the post-operative lung function between transplant

Table 2. Lung function and perfusion rate to the transplanted lung before and after lung transplantation in patients with scleroderma in our pulmonary institute (n = 7)

Patient no.	FVC, % (l)		FEV1, % (l)		TLC, % (l)		DLCO, %		SAT O_2, % Rest		Exercise, % Post		Perfusion, %	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	106 (3.0)	113 (3.2)	99 (2.4)	101 (2.4)	94 (4.3)	117 (5.4)	16	36	86	99	82	96	54	67
2	36 (1.3)	49 (1.5)	34 (1.2)	47 (1.9)	49 (3.1)	47 (2.9)	21	24	93	97	81	95	50	63
3	45 (1.5)	–	42 (0.94)	–	53 (2.2)	–	24	–	85	–	82	–	49	–
4	46 (1.8)	54 (2.1)	51 (1.6)	55 (1.7)	63 (3.8)	65 (3.9)	19	38	87	99	82	99	33	67
5	37 (0.88)	51 (2.4)	37 (0.74)	51 (2.0)	60 (2.48)	70 (2.9)	46	68	92	98	83	96	44	68
6	63 (1.8)	72 (1.9)	69 (1.7)	75 (1.8)	64 (3.0)	72 (3.4)	21	38	93	98	87	94	50	72
7	50 (1.3)	54 (1.4)	41 (0.9)	56 (1.3)	56 (2.3)	75 (3.1)	28	46	97	98	94	97	60	85

DLCO, diffusion capacity of carbonic monoxide; FEV1, forced expiratory volume in one s; FVC, forced vital capacity; LTX, lung transplantation; Sat O_2, oxygen saturation; TLC, total lung capacity.

Table 3. Lung transplantation in patients with scleroderma: review of the literature

Reference	No. of patients	Mean age (yr)	Sex (female:male)	Pulmonary HTN, n (%)	Pulmonary fibrosis, n (%)	Type of LTX	Post-LTX FEV1 (%)	Follow up (months)	One-yr survival (%)
Massad et al. (8)	47	46.4	27:20	NA	NA	27 SLT, 20 DLT	NA	36	67
Present report	7	52	5:2	6 (84)	7 (100)	7 SLT	56	8	86

DLT, double-lung transplantation; FEV1, forced expiratory volume at one s; HTN, hypertension; LTX, lung transplantation; SLT, single-lung transplantation.

recipients with and without scleroderma noted any differences between the two groups. Accordingly, both studies (1, 6) that compared the rates of infection (bacterial, viral, and fungal) and rejection between lung transplant recipients with and without scleroderma found a similar incidence in the two groups.

In all the studies, including the present series, the survival rate of the scleroderma patients was similar to that of other lung transplant recipients. A total of 23 patients (42%) died. Early deaths (< 30 post-LTX) were reported in 13 patients (24% of all patients and 56% of the deaths) and late deaths in 10 patients. Infections and graft failure were the most common causes of death (Table 4). In our series, four patients died in the two months following the transplantation and two other recipients during the five months following the transplantation. The two- and five-yr survival rates were 72% and 55%, respectively.

Discussion

The timing of referral for prospective transplantation in appropriate lung transplant candidates has always been and remains a moving target. The careful consideration of the natural history and prognosis of the underlying primary disease, the scleroderma, needs to be weighed against the projected survival time post-transplant (10). To the best of our knowledge, our study is the first to summarize the clinical and survival data in the literature on LTX in patients with scleroderma.

Pulmonary fibrosis and pulmonary HTN are the two most common complications of scleroderma lung disease, occurring in 70% and 50% of patients, respectively (4). Both can lead to severe disability and death. Therefore, LTX should be performed in selected patients with severe disease. However, because of the various organ failures associated with scleroderma, special attention must be addressed to evaluating candidates for LTX.

Contraindications for LTX

Certain co-morbidities associated with scleroderma are considered contraindications to LTX (1). Although no center-specific inclusion and exclusion criteria for transplantation in patients with scleroderma were mentioned in the various case reports (1, 5–9), in general, patients with end-stage lung disease who also manifested overt symptoms of systemic disease were not considered good candidates (Table 5).

The skin involvement in scleroderma may range from limited to mild to severe cutaneous thickening. Skin breakdown due to ulceration may be localized or spread over joints or larger areas subject to pressure (1). Because it predisposes patients to

Table 4. Causes of early and late mortality in 54 patients with scleroderma who underwent lung transplantation

Cause of death	No. of patients
Early mortality (<30 d)	
Graft failure	5
Bacterial infection	4
Cardiac event	2
Hemorrhagic stroke	1
No recorded	1
Late mortality (>30 d)	
Bacterial infection	4
Respiratory failure	2
Viral infection	2
Graft failure	1
Cardiac event	1
Total	23

Table 5. Suggested criteria for lung transplantation in patients with scleroderma

1. Severe pulmonary fibrosis (FVC and DLCO <40%), unresponsive to medical treatment
2. Absence of severe pulmonary HTN (mean PAP < 45 mmHg)
3. Creatinine clearance above 50 mL/min
4. Absence of severe skin involvement (severe cutaneous thickening)
5. Absence of severe esophageal dysmotility and aspiration
6. Absence of large pericardial effusion
7. Absence of significant conduction abnormalities (symptomatic bradycardia, atrial, and ventricular tachycardia)
8. Absence of severe small intestine, gastroparesis, colorectal and rectum involvement such as pseudo-obstruction, diverticulitis, and perforation

FVC, forced vital capacity; DLCO, diffusion capacity of carbonic monoxide; HTN, hypertension.

infection, significant skin breakdown was considered a relative contraindication to LTX in most of the studies (1). Some authors also suggested that the tendon retraction and deformity secondary to skin breakdown in the diffuse form of scleroderma may limit patient mobility and consequently have a negative impact on the post-transplant rehabilitation process (1). Our experience showed that carefully selected patients with scleroderma skin involvement including patients with Raynaud's phenomenon without infection (n = 2) can successfully undergo LTX.

Renal dysfunction often affects patients with scleroderma, and many of the common immunosuppressive agents, such as calcineurin inhibitors, are nephrotoxic. Therefore, a creatinine clearance below 50 mL/min has been proposed as a contraindication for LTX (1). However, some patients with severe pulmonary HTN and right heart dysfunction may present with a reduced creatinine clearance because of poor cardiac output, without significant endogenous renal disease. Occasionally, this problem can be managed with judicious use of diuretics and vasodilator therapy. Additionally, low-dose dopamine in conjunction with vasodilators may improve renal function and serve as a bridge to transplantation (11).

Esophageal dysmotility and gastroparesis, both typically seen in patients with scleroderma, can lead to gastroesophageal reflux disease and aspiration. Scleroderma patients with a history of aspiration are often considered poor candidates for LTX owing to the risk of aspiration pneumonia. More recently, post-LTX gastric fundoplication has been advocated to minimize reflux-related pulmonary complications (9, 12). However, because of the poor esophageal motility, other surgery like partial wraps should be considered.

Because esophageal involvement occurs in 50–80% of patients with scleroderma, all patients being considered for LTX should undergo formal testing to exclude severe esophageal disease and aspiration potential. Manometry appears to be superior to pH-metric testing in assessing the degree of reflux severity (13). Cine-esophagrams may help to detect esophageal dysmotility. It should be stated that severe esophageal dysmotility with aspiration are contraindications for LTX. Therefore, scleroderma patients with normal esophageal gastroscopy or patients with mild esophagitis could be on the waiting list for LTX. Involvement of the small intestine, colon, and rectum may lead to significant complications, such as pseudo-obstruction, diverticulitis, and perforation, all of which can complicate LTX.

The cardiac involvement in scleroderma includes rhythm conduction abnormalities, myocardial disease, and pericardial disorders. The conduction abnormalities are thought to be a consequence of diffuse myocardial fibrosis. Atrial and ventricular arrhythmias are present in 5–10% of patients with scleroderma (14). Significant arrhythmias should be considered a contraindication for LTX.

The rate of myocardial fibrosis in autopsy studies is about 60%. However, less than one-third of patients have significant left ventricular dysfunction (15, 16), and most of these have diffuse scleroderma.

Right ventricular failure is more common in limited scleroderma. The right ventricle tends to recover in size and function after the drop in mean pulmonary pressure in the early post-transplant period (17, 18). Therefore, right ventricular dysfunction, by itself, is not a contraindication for LTX. However, patients with advanced myocardial fibrosis and left ventricular dysfunction should not undergo LTX, although they may be suitable candidates for heart-lung transplantation.

Summary

In summary, the decision to perform LTX in patients with extra-pulmonary disease must be individualized and based on the clinical course of their disease. Patients should be excluded from consideration of transplantation if they have severe or progressive systemic involvement.

Although double-lung transplant recipients have better pulmonary function than single-lung transplant recipients (19), exercise performance is similar in both groups (19, 20). This finding has made SLT the procedure of choice for most patients, especially in view of the dearth of donor lungs. The procedure of choice for patients with scleroderma has not been determined, but SLT proved adequate in most of the reported cases (Table 3). Nevertheless, DLT is becoming more attractive because of the long-term problems in the native lung such as cancer to which scleroderma patients are at risk. In patients with severe pulmonary HTN without pulmonary fibrosis that met all other criteria, heart-lung transplantation could be a possible alternative.

There are few data in the medical literature directly addressing the outcome of LTX in patients with scleroderma. On the basis of our series as well as the reported single- and multi-center studies, there appear to be no differences in early and late mortality rates between patients with scleroderma and patients after LTX for other indications. The two- and five-yr survival rates for the 54

scleroderma patients analyzed in the present study were 72% and 55%, respectively. These rates are similar to the 70% and 49% rates, respectively, reported by the registry of the ISHLT (21).

Conclusion

LTX is a valid option for patients with scleroderma and progressive end-stage pulmonary dysfunction that is unresponsive to medical therapy. Patients with severe systemic involvement should be excluded. The procedure of choice so far is SLT. The short- and long-term outcomes of patients with scleroderma are apparently similar to the outcomes of patients undergoing LTX for other conditions.

Conflict of interest

None.

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