

RECURRENCE OF SARCOID GRANULOMAS IN LUNG TRANSPLANT RECIPIENTS IS COMMON AND DOES NOT AFFECT OVERALL SURVIVAL

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ABSTRACT. *Background:* Sarcoidosis represents 2,5% of all indications for lung transplantation and criteria are generally assumed to be the same as for pulmonary fibrosis. Recurrence of granulomas in transplanted lungs has earlier been proved to derive from recipient immune cells, but its role in relation to lung function and overall survival after lung transplantation remains uncertain. *Objective:* To identify recurrent granuloma in transbronchial biopsies in patients receiving lung transplant because of sarcoidosis, and relate the findings to overall survival and lung function. *Design:* A total of 620 patients were transplanted at this centre from 1992 until august 2012. This study comprised all patients (n=25) transplanted due to pulmonary sarcoidosis. Lung functions, trans-bronchial biopsies, and survival were compared in patients with and without recurrence of granulomas. Granulomas were defined as non-necrotizing epitheloid granulomas with multinucleated giant cells according to standard criteria (formation of epitheloid giant cells) without presence of infection. *Conclusions:* Approximately 30% of lung transplant recipients due to sarcoidosis have recurrence of sarcoid granulomas. Recurrence of granulomas does not affect overall survival or lung function. (*Sarcoidosis Vasc Diffuse Lung Dis* 2014; 31: 149-153)

KEY WORDS: Transplantation; Sarcoidosis; Biopsies

INTRODUCTION

Sarcoidosis generally is a benign disease with more than 2/3 of all cases undergoing spontaneous remission, but up to 30% show chronic or progressive disease which in a small fraction of patients develops into life threatening disease with end-stage organ failure and death(1). According to data from the International Society of Heart and Lung Trans-

plantation (ISHLT registry), sarcoidosis represented 2,5% of all indications for lung transplantation worldwide from January 1995 to June 2011, and the number seems to be increasing. There are no specific selection criteria for patients suffering from sarcoidosis reviewed for lung transplantation, but selection criteria are widely regarded as being the same as for Idiopathic Pulmonary Fibrosis (IPF) (2,3).

Recurrence of sarcoid granulomas in donor lungs has earlier been described, and it has been proven that recurrence of sarcoid granulomas is derived from the recipient's immune cells (4,5). No studies have been published investigating the importance of sarcoid granulomas in regards to loss of lung function and overall survival after lung transplantation, and a study published on survival have been with small population size and short follow-up time (6).

Received: 18 June 2013

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Methods

Single-center retrospective study from a national lung transplant center comprising all 620 lung transplant recipients from 1992-2012, including all 25 patients (17 men and 8 women) with pulmonary sarcoidosis. Diagnosis was secured before transplantation by biopsy and re-assured through histopathological examination of explanted lung. Data were retrieved through patient files. A retrospective study without intervention does not require permission from The National Committee on Health Research Ethics, but permission was obtained from the Danish Data Protection Agency for the storage and use of data.

Selection of donors and recipients, the transplant procedure, induction therapy and maintenance immunosuppression and antibiotic prophylaxis, as well as the follow-up programme has been described earlier in detail (7-9).

This centre has maintained the same comprehensive surveillance bronchoscopy programme with transbronchial biopsies for all patients at 2,4,6,12 weeks, 6,12,18,24 months. 5-8 trans bronchial biopsies were obtained per bronchoscopy, preferable from the middle lobe.

Biopsy specimens were fixed in formalin and processed into a paraffin block within a few hours by microwave technique. Histologic specimens were obtained by serial cutting at 3 µm. four to six sections were placed on each of the 12 slides routinely used for histologic analysis. Details for histopathological preparation at this centre have been described earlier (10). Histologic evaluation was performed by a single pathologist (CBA) according to the standard criteria(11).

All trans-bronchial biopsies including pathological examination of explanted lungs were reviewed. The biopsies were graduated using ISHLT guidelines regarding rejection of lung allografts(12), and with regards to recurrence of non-necrotizing giant cell epithelioid granulomas in donor lungs. Patients were divided into two groups: Group A (n=7) included patients with sarcoidosis who did have recurrence of sarcoid granulomas. Group B (n=18) included patients with sarcoidosis who did not have recurrence of sarcoid granulomas.

None of the patients in showed radiological evidence of recurrent sarcoidosis, and they were not evaluated by EBUS.

All patient spirometries as well as all patient pulmonary plethysmographs were revisited. The baseline FEV₁ was calculated as the average of the two best measures of FEV₁ obtained post-transplantation on two separate occasions 3 weeks apart, in accordance with internationally accepted criteria, and the last FEV₁ recorded were also obtained, to calculate the BOS grade(13).

Statistical analysis was performed with SPSS 19, using Mann-Whitney or Fisher's exact test to show differences, and Kaplan-Meier plot and Log-Rank test to show survival. P < 0.05 was considered statistically significant.

The study was supported by Copenhagen University Hospital, Rigshospitalet, The Heart Centre Research Foundation and from an unrestricted research grant from Intermune.

Results

A total of 25 patients with sarcoidosis were lung transplanted from 1992 to September 2012. Table 1 shows basic demographic information between the 2 groups.

Median follow up time was 6,1 (,31-15,37) years for the non-granuloma group and 3,8 (1,83-1,87) for the group encountering recurrence of sarcoid granulomas.

The 2 groups were equal regarding age, height and weight. There was no difference in the distribution of sex in the groups P=0,277 using Fisher's exact test. 37,5% of female patients had recurrence of sarcoid granuloma, 23,5% of male patients had recurrence of sarcoid granuloma. Baseline lung function and pretransplant medication were not significantly different (Table 1). Pulmonary haemodynamics were not statistically significant (data not shown).

During the 2 year trans-bronchial biopsy surveillance programme after transplantation, granuloma was first seen at a median of 189 (163-453) days after transplantation. Granulomas were persistent in 13 out of 22 of the following surveillance trans-bronchial biopsies in the 7 patients who had recurrence of non-necrotizing giant cell epithelioid granulomas. Figure 1 shows recurrent granuloma in transplanted lung, and table 2 shows biopsy findings in the seven patients with recurrence of granulomas.

Table 1. Baseline lung function and pretransplant medication

	Granulom (n=7) Median (range)	Non-granulom (n=18) Median (range)	P-Value
Age at transplantation (years)	45,9 (41-58)	51,7 (36-58)	,270
Height (m)	1,74 (1,71-1,86)	1,74(1,56-1,93)	,799
Weight at transplantation (kg)	88 (45-98)	68 (42-95)	,266
Prednisolon dose (mg)	11,25 (0-20)	7,5 (0-50)	,519
Azathioprin dose (mg)	0 (0-100)	0 (0-150)	,910
FVC (pretransplantation)	1,8 (1-3,4)	1,76 (1,1-2,92)	,306
FEV1 (pretransplantation)	,89 (.55-2,58)	,86 (.50-2,19)	,820
Best FEV1	2,15(.65-4,29)	1,90(1,05-4,0)	,458
Last obtained FEV1	2,16 (0,55-4,06)	1,37 (.68-3,40)	,389
DLCO after 6 months	1,0 (.80-1,30)	1,1 (.65-1,8)	,123
DLCO after 12 months	1,0 (0,8-1,4)	1,17 (.67-1,9)	,485
TLC pretransplantation	4,80 (4,06-7,08)	5,82 (2,49-9,20)	1,0
TLC after 6months	5,0 (3,2-7,1)	5,0 (2,7-6-9)	,671
TLC after 12 months	5,1 (3,0-7,4)	5,3 (2,95-7,4)	,699

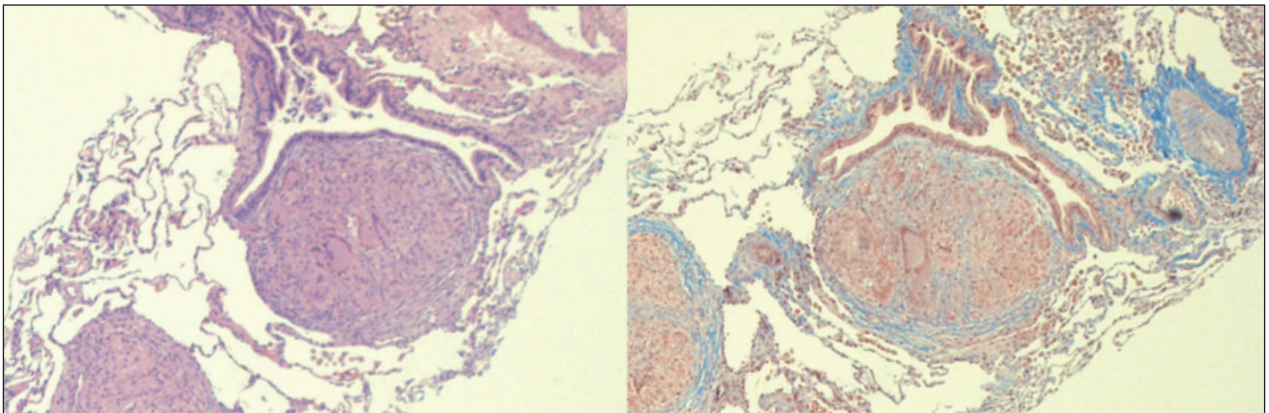


Fig. 1. Biopsy from middlelobe in double lung transplant recipient. A.HE staining and B (C4d staining) Masson-Trichrome staining showing recurrent non-necrotizing granulomas (of several granuloma, showing characteristic features) with multinucleated giant cells along the bronchovascular bundles.

There was no statistical difference between baseline FEV₁ (P=0,458) and last recorded FEV₁ (P=0,389) in the two groups. There was no statistical difference between diffusion capacity at 6 and 12 months (P=,123) and (P=,485) and no statistical difference in TLC at 6 and 12 months (P=,671) and (P=,699). Also shown in table 1.

Survival between the two groups is shown as a Kaplan-Meier plot in figure 2. Log Rank (Mantel-Cox) was P=0,399.

Discussion

The long term out-comes after lungtransplantation for end-stage sarcoidosis is comparable to long-term outcomes for IPF (14, 15). We found recurrence of sarcoid granulomas to be common, but it does not affect survival or lung function. Both regarding dynamic flow volumina and regarding total lung capacity and diffusion capacity.

In our cohort we found that patients receiving lung transplant due to end-stage sarcoidosis, have an approximately 30% overall risk of having recurrence

Table 1. Baseline Table

Patient	2 weeks	4 weeks	6 weeks	12 weeks	6 months	12 months	18 months	24 months
1	0	0	0	0	X	0	?	?
2*	0	0	0	0	X	0	0	?
3	0	0	0	0	X	X	0	0
4	0	0	0	0	X	X	0	0
5	0	0	0	0	X	X	0	X
6	0	0	0	0	0	X	X	X
7	0	0	0	0	0	0	X	0

X= non-necrotizing giant cell epithelioid granuloma 0=no granuloma ?= missing data due to early death.

*The patient has had two extra biopsies taken out of protocol, at 9 months and 10 months, both showing no of non-necrotizing giant cell epithelioid granuloma

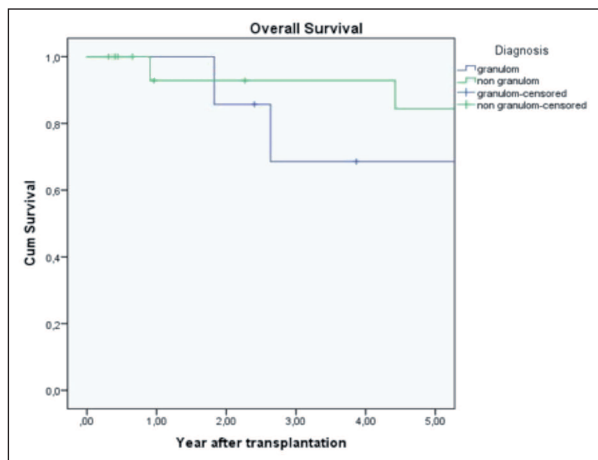


Fig. 2. Recurrence of sarcoid granulomas in lung transplant recipients is common and does not effect overall survival.

of non-necrotizing giant cell epithelioid granuloma. These numbers may be considerable higher due to small biopsy samples, and the sensitivity in the use of trans-bronchial biopsies as a diagnostic tool to find recurrent disease. Recurrence of sarcoidosis has been described in numerous studies earlier. To the best of our knowledge the frequency of recurrent sarcoidosis in transplanted lungs has not earlier been described as well as the morbidity and mortality consequences of recurrence has not earlier been described.

We have consecutive biopsies on patients showing the value of trans-bronchial biopsies as a diagnostic tool in sarcoidosis showing a sensitivity of 7/15 biopsies after first recurrence of granuloma.

Some studies suggests that the use of trans-bronchial biopsies has a sensitivity 30-50% depending of severity of sarcoidosis (16,17), another study

suggest a diagnostic accuracy rate of up to 80%(18). This explains the non-persistency of sarcoid granulomas in our population.

Usual immunosuppressant medication after lung transplantation exceeds the guidelines for management of sarcoidosis(19-22). The immunosuppressant medication after lung transplantation usually contains of prednisolon, a calcineurin inhibitor and mycophenolat mofetil or azathioprin. There has been little evidence earlier (23, 24) suggesting that patient with severe uncontrolled sarcoidosis benefit from calcineurin-inhibitors and mycophenolat mofetil.

Even though it is the recipient's immune cells colonizing the lung allograft, it does not affect the overall survival; neither does it affect the overall lung function compared to transplant recipients who did not encounter recurrence of sarcoid granuloma.

In this study the recurrence of epithelioid granuloma is a not a prognostic factor for loss of lung function or overall survival in lung transplant recipients, and if that corresponds to patients with sarcoidosis not receiving lung transplantation, the results from this study suggests that in general patient with aggressive sarcoidosis are not sufficiently treated with immune suppressant medication, and a more aggressive approach could possibly keep a higher number of patients from being transplanted.

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