DIFFERENT CHRONIC ALLOGRAFT PATHOLOGY LESIONS IN TWO ORTHOTOPIC LUNG TRANSPLANT RAT STRAIN COMBINATIONS

Federica Pezzuto[1], MD, Francesca Lunardi[1], MD, PhD, Marta Vadori[2], PhD, Davide Zampieri[1], MD, Federica Casiraghi[3], PhD, Stefania Edith Vuljan[1], ScD, Marco Mammana[1], MD, Marco Schiavon[1], MD, PhD, Emanuele Cozzi[1], MD, PhD, Federico Rea[1], MD, Fiorella Calabrese[1], MD

[1]University of Padova Medical School, Padova Italy

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INTRODUCTION

- Chronic lung allograft dysfunction (CLAD) remains an obstacle to long-term survival after lung transplantation

ELSEVIER

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Chronic lung allograft dysfunction: Definition, diagnostic criteria, and approaches to treatment—A consensus report from the Pulmonary Council of the ISHLT

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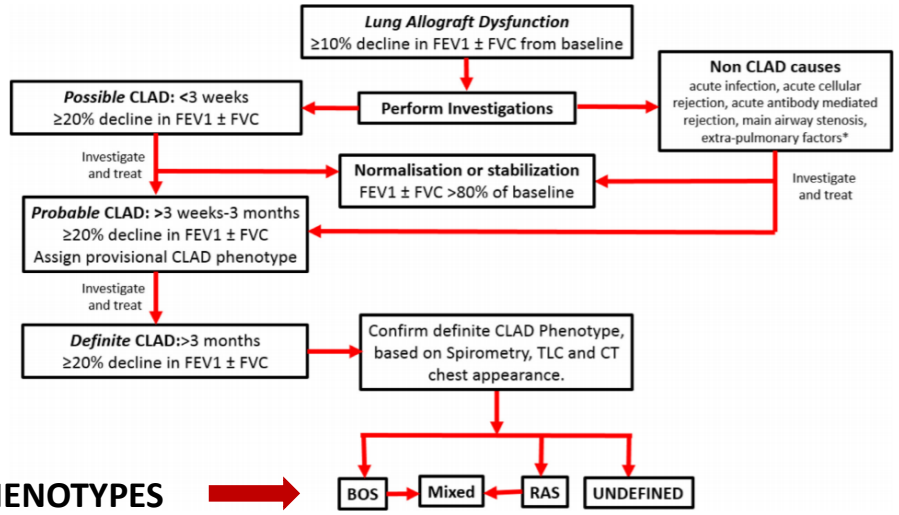


CLAD PHENOTYPES

PRECLINICAL MODELS

- The orthotopic lung transplantation model in rodents remains the best model animal to study
- Numerous technical refinements were made to improve the reproducibility of end point
- Successfully used to reproduce OB aspects in orthotopic lung transplantations in a few rat models
- Nonetheless, the use remains limited in the literature

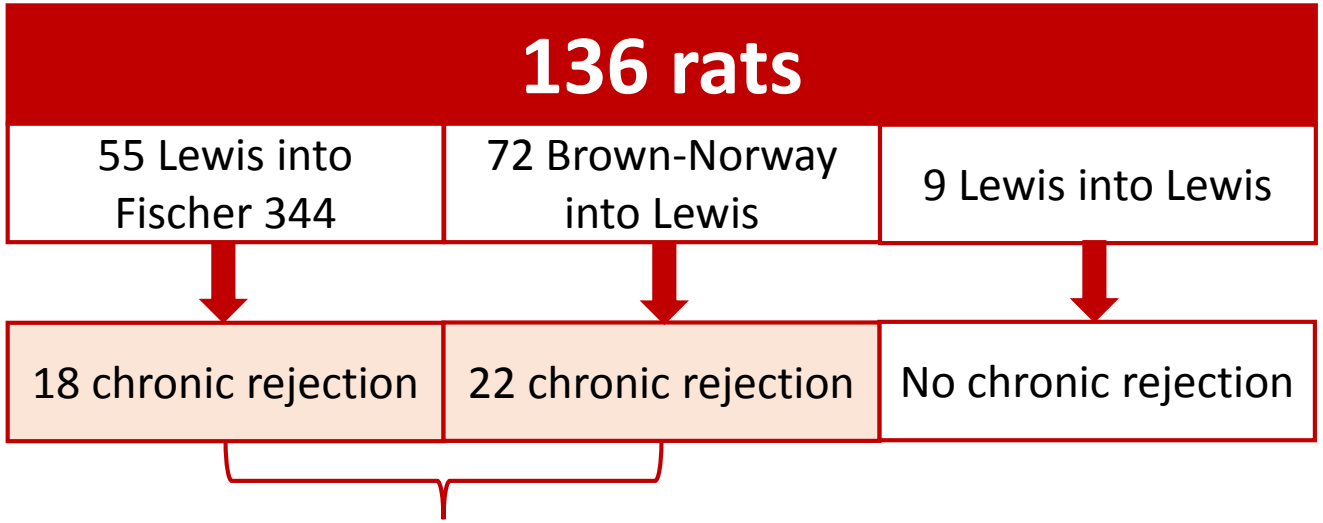
PURPOSE

- **PRIMARY AIM**: to investigate if all the histological changes reported as important in clinical CLAD can be found in rat orthotopic lung transplants
- **SECONDARY AIM**: to compare the histological CLAD lesions of the two animal models in order to identify any difference between them

METHODS

Rat orthotopic lung transplants performed in our center from 2007 to 2017

STUDY POPULATION



Histological review taking into consideration the new knowledge we have on human CLAD histological lesions, in particular those usually detected in BOS or RAS

HISTOLOGY

A. PERI-AIRWAY FIBROSIS
B. OBLITERATIVE AIRWAY FIBROSIS
C. PARENCHYMAL FIBROSIS
D. PLEURAL FIBROSIS
E. LYMPHOID AGGREGATES
F. ENDOTHELIITIS
G. VASCULAR FIBROSIS
H. EPITHELIAL HYPERPLASIA
I. EPITHELIAL FLATTENING

SCORE 0
SCORE 1
SCORE 2
SCORE 3
SCORE 4

LOW GRADE
HIGH GRADE

TIME OF SACRIFICE

EARLY (1 week)
INTERMEDIATE (2 weeks-2 months)
LATE (>2 months)
EARLY (1 week)
INTERMEDIATE (2 weeks-2 months)
LATE (>2 months)

Spectrum of chronic lung allograft pathology in a mouse minor-mismatched orthotopic lung transplant model

Am J Transplant. 2019;19:247–258.

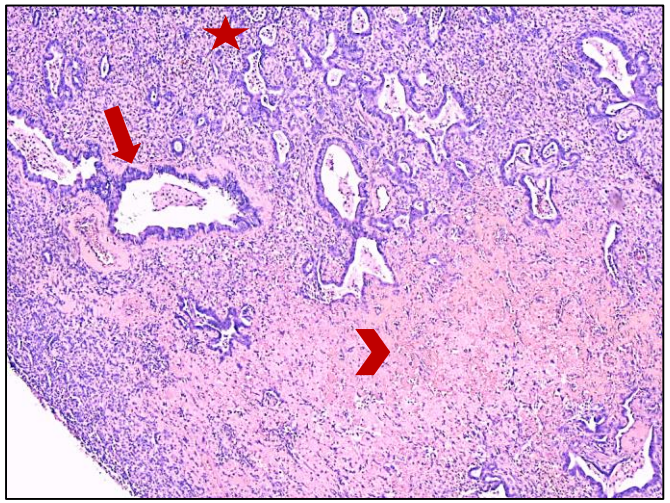
STATISTICAL ANALYSIS

- Data were expressed as mean ± standard deviation
- Group comparisons were assessed with robust permutation tests: Exact General Independence Test for ordered categorical and continuous variables and Exact Linear-by-Linear Association Test for dichotomous variables using the {coin} R package
- Pathological parameters were also categorized following the times of sacrifice. Since in G2 no rats survived up to 90 days, the comparison was made only between “early” and “intermediate” timepoints for this group
- Competing risk analysis was performed using the {cmprsk} R package to compare high-grade histological findings, taking into account the different times of sacrifice of each rat. R v.3.6.2 was used for the analysis

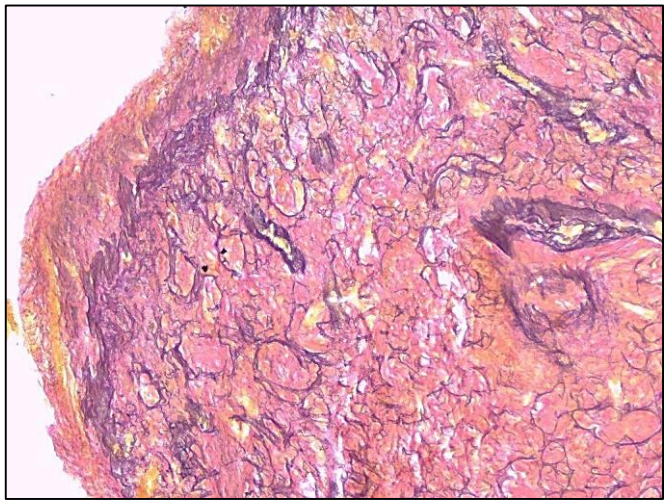
RESULTS

PARAMETER	RATS (N=40)	G1 RATS (N=18)	G2 RATS (N=22)	P-VALUE
ACR [N (%)]	7 (17.5%)	4 (22.2%)	3 (13.6%)	***0.679***
Peri-Airway Fibrosis (Mean±SD)	2.14±1.28	2.17±1.19	2.10±1.45	***1.000***
Obliterative Airway Fibrosis (Mean±SD)	1.14±0.99	1.00±1.13	1.30±0.82	***0.541***
Parenchymal Fibrosis (Mean±SD)	26.6±18.0	22.5±18.3	31.5±17.3	***0.266***
Pleural Fibrosis (Mean±SD)	2.73±1.45	2.58±1.56	2.90±1.37	***0.667***
Lymphoid Aggregates (Mean±SD)	0.59±1.01	1.08±1.16	0.00±0.00	***0.004****
Endotheliitis (Mean±SD)	2.23±1.23	1.58±0.90	3.00±1.15	***0.007****
Vascular Fibrosis (Mean±SD)	2.64±1.18	2.17±0.72	3.20±1.40	***0.043****
Epithelial Hyperplasia (Mean±SD)	0.73±0.77	0.92±0.90	0.50±0.53	***0.284***
Epithelial Flattening (Mean±SD)	0.95±1.43	0.83±1.53	1.10±1.37	***0.580***

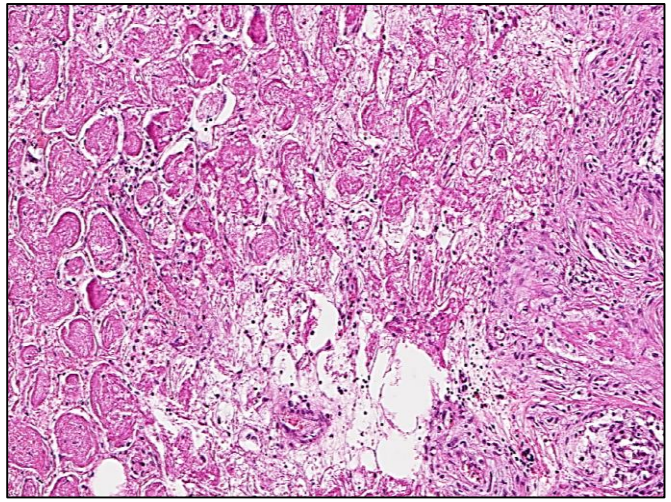
RESULTS



END STAGE OB
2 cases in G1



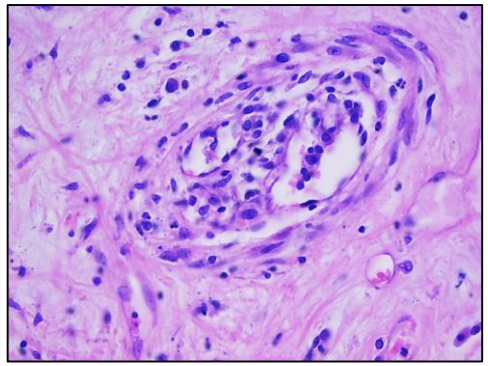
END STAGE RAS
4 cases in G1
12 cases in G2

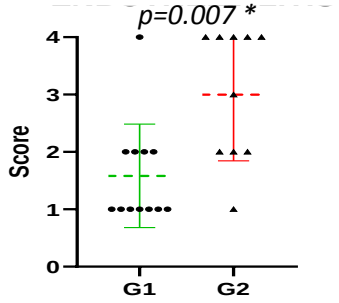


AFOP
2 cases of G2

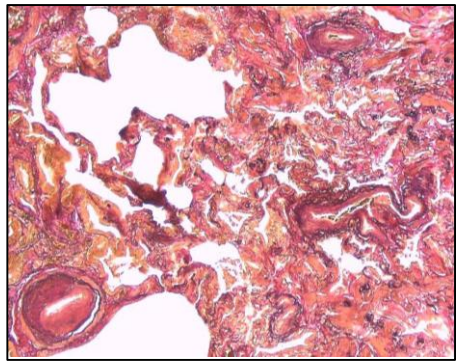
RESULTS

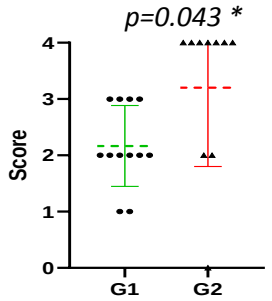
ENDOTHELIITIS



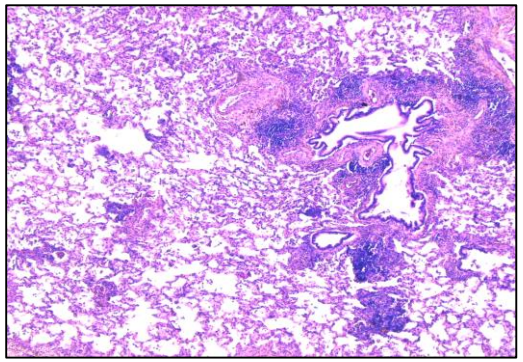


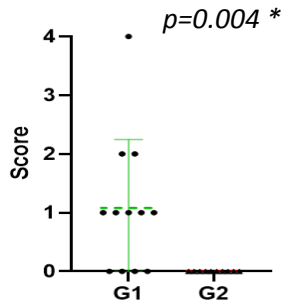
VASCULAR FIBROSIS





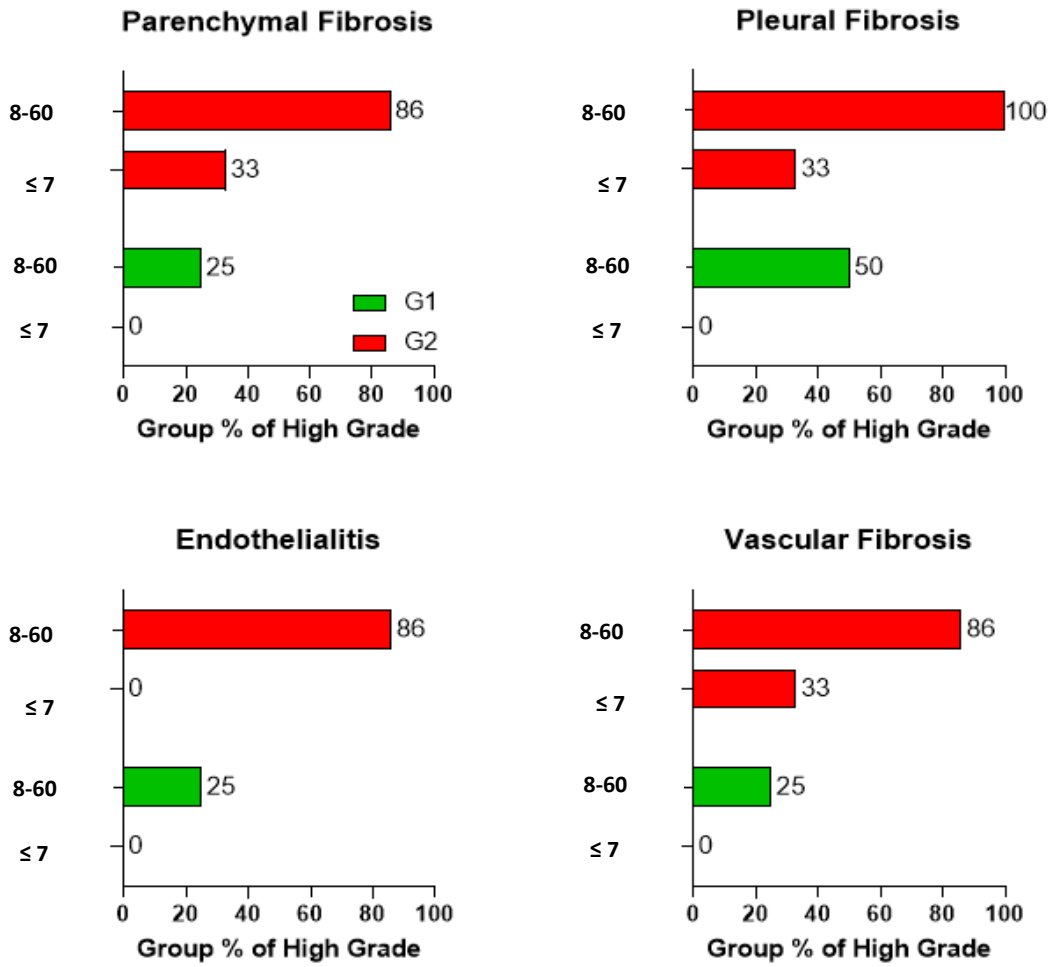
LYMPHOID AGGREGATES





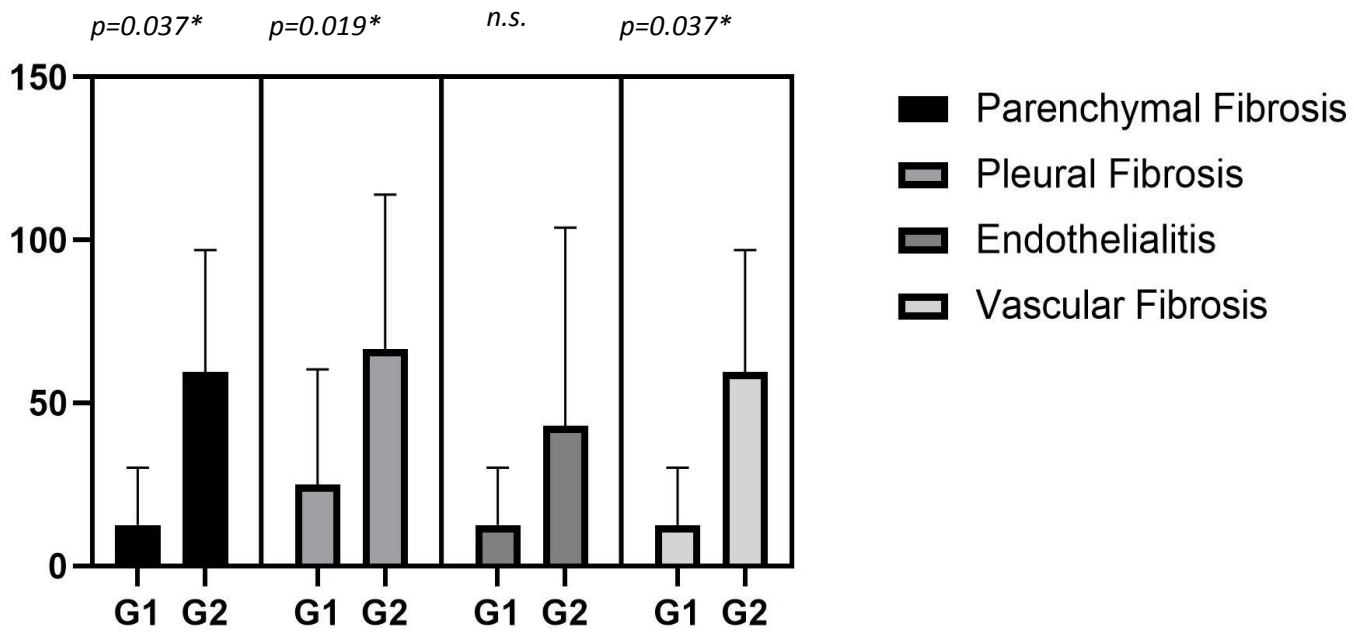
A statistically significant difference between G1 and G2 scores was found for endotheliitis, vascular fibrosis and lymphoid aggregates

RESULTS



High-grade parenchymal fibrosis, pleural fibrosis, endotheliitis, and vascular fibrosis were mostly detected in G2 rats and appeared earlier compared to the G1 group

RESULTS



The results of competing risk analysis showed that the differences between G1 and G2 were statistically significant for parenchymal, pleural and vascular fibrosis

CONCLUSIONS

- Lewis into Fischer 344 and Brown-Norway into Lewis rats represent two orthotopic lung transplant rat strain combinations that show allograft pathological lesions similar to the human alterations detected in CLAD
- Brown-Norway into Lewis showed more frequent RAS-like CR lesions, a finding that could be related to a higher degree of mismatch in this strain combination
- The recent proposed grading system has been shown to be extremely useful in the study of CR pathological lesions, leading to the identification of crucial differences between rat experimental model strains
- Should our findings be confirmed by further experimental studies, these two rat strain combinations could represent valuable animal models for better understanding CLAD pathogenetic mechanisms and possibly help identify appropriate treatment strategies