

Histopathological Findings Associated With Gastroesophageal Reflux Disease and Aspiration After Lung Transplantation: Initial Brazilian Single-Center Experience

R.M. Carraro^{a,*}, E.C.T. Nascimento^b, S. Szachnowicz^d, P.C.L.B. Camargo^a, S.V. Campos^a, J.E. Afonso Jr.^a, M.N. Samano^c, P.M. Pêgo-Fernandes^c, M. Dolhnikoff^b, R.H.O.B. Teixeiraa^a, and A.N. Costa^a

^aPulmonary Division, Heart Institute (InCor), University of Sao Paulo Medical School, Sao Paulo, Sao Paulo, Brazil; ^bDepartment of Pathology, University of Sao Paulo Medical School, Sao Paulo, Sao Paulo, Brazil; ^cThoracic Surgery Division, Heart Institute (InCor), University of Sao Paulo Medical School, Sao Paulo, Sao Paulo, Brazil; and ^dEsophageal Surgical Division, Hospital das Clinicas, University of Sao Paulo Medical School, Sao Paulo, Sao Paulo, Brazil

ABSTRACT

Background. Gastro-esophageal reflux disease (GERD) and broncho-aspiration (BA) are known to increase the risk for chronic lung allograft dysfunction (CLAD). However, specific lung injury mechanisms are not clearly known. The objective of the study was to describe histopathological findings in surveillance lung transbronchial biopsies that can be correlated with episodes of BA in the lung allograft.

Methods. This retrospective analysis of surveillance transbronchial biopsies was performed in lung transplant recipients, with available data of broncho-alveolar fluid (cultures and cytology), lung function parameters, and esophageal functional tests.

Results. Were analyzed 11 patients, divided into 3 groups: (1) GERD group: 4 patients with GERD and CLAD diagnosis; (2) control group: 2 patients without GERD or CLAD; and (3) BA group: 5 patients with foreign material in lung biopsies. A histopathological pattern of neutrophilic bronchitis (NB) was present in 4 of 4 cases in the GERD group and in 1 of 5 cases in the BA group in 2 or more biopsy samples; culture samples were all negative; the 5 NB-positive patients developed CLAD and died (3/5) or needed re-transplantation (2/5). The other 3 patients in the BA group had GERD without NB or CLAD. Both patients in the control group had transient NB in biopsies with positive cultures but remained free of CLAD.

Conclusions. Surveillance transbronchial biopsies may provide useful information other than the evaluation of acute cellular rejection and can help to identify high-risk patients for allograft dysfunction related to gastro-esophageal reflux.

CHRONIC lung allograft dysfunction (CLAD) is the major limiting factor of long-term survival after lung transplantation [1]. Among multiple different contributors, gastro-esophageal reflux disease (GERD) is established as a risk factor for its development [2,3], with a greater prevalence among both lung transplant candidates and recipients [4,5].

In the past decades, many centers have been studying this relationship between GERD and CLAD, mostly on the basis of function esophageal tests and broncho-alveolar

lavage (BAL) samples with gastric or biliar enzyme content [6–8]. Besides that, surgical treatment for GERD is actually considered the best choice for prevention or treatment of lung dysfunction related to GERD and broncho-aspiration (BA) [3].

*Address correspondence to Rafael Medeiros Carraro, Av. Doutor Enéas de Carvalho Aguiar, 44, Jardim Paulista, São Paulo 05403-900, Brazil. E-mail: carraro.rafael@gmail.com

Table 1. Clinical Characteristics and Outcomes of Groups 1 and 2

| | Age (y) | Type of Procedure | Lung Disease | ACR (n) | NB | Other Pathological Findings | Outcome | BAL Neutrophils | BAL Culture |
|--------|---------|-------------------|--------------------------|---------|-----|-----------------------------|---------------------|-----------------|-----------------------|
| GERD+ | | | | | | | | | |
| CLAD+ | | | | | | | | | |
| Case 1 | 63 | Unilateral | Interstitial disease | 3 | Yes | | Death | 15% | Negative |
| Case 2 | 59 | Unilateral | Interstitial disease | 2 | Yes | Organizing pneumonia | Death | 60% | Negative |
| Case 3 | 46 | Unilateral | Emphysema | 3 | Yes | | Death | 50% | Negative |
| Case 4 | 36 | Bilateral | Bronchiectasis | 2 | Yes | | Re-transplant | 5% | Negative |
| GERD- | | | | | | | | | |
| CLAD- | | | | | | | | | |
| Case 1 | 50 | Bilateral | Lymphangioleiomyomatosis | 0 | Yes | Organizing pneumonia | CLAD absent (77 mo) | 60% | <i>P aeruginosa</i> |
| Case 2 | 20 | Bilateral | Cystic fibrosis | 2 | Yes | None | CLAD absent (60 mo) | 35% | <i>Aspergillus sp</i> |

Recognition of foreign material in lung tissue allows a definitive diagnosis of BA; however, it is not present in the totality of BA cases. Outside the scope of lung transplantation, aspiration has been also strongly associated with chronic interstitial disease [9,10]. Mechanisms of lung allograft injury secondary to BA are not completely understood; acute cellular rejection (ACR) triggering and chronic bronchiolar inflammation are hypothesized as possible pathways [11], but there is still no description of specific histopathological pattern that correlates aspiration and evolution to lung allograft dysfunction.

The aim of this study was to describe pathological patterns beyond ACR that could represent a pathway of lung allograft dysfunction related to BA.

METHODS

We retrospectively revised, among recipients who had lung transplantation between January 2003 and June 2015, all surveillance lung biopsies of patients who met inclusion criteria as follows: (1) minimum period of 12-month follow-up after lung transplant and (2) available data from esophageal functional tests and lung function tests. Patients with diagnosis of bronchial stenosis were not included in the study.

Epidemiological data and lung function tests were collected from patients' charts. Diagnosis and severity graduation of CLAD were made according to the last *International Society for Heart and Lung Transplantation* (ISHLT) published consensus [2,3].

Lung Biopsy Reviews

Bronchoscopies with transbronchial biopsies were performed as established by local protocol within 2 to 6 weeks after transplantation and then 3, 6, 9, and 12 months after the procedure, as

well as at any other time if necessary according to clinical judgment. Culture and cytological BAL samples were also collected at the same time and included in the analysis.

All biopsies were revised by a lung pathologist. Description of findings regarding ACR was reported according to the standardization of the last guideline published of the ISHLT [12]. In addition, the following histopathological findings were systematically evaluated in all the cases reviewed: neutrophilic bronchitis, chronic bronchitis, organizing pneumonia, bronchiolitis obliterans, aspiration bronchitis/bronchiolitis, foreign-body reaction, diffuse alveolar damage, bronchopneumonia, and bronchiolocentric pulmonary fibrosis.

Esophageal Functional Evaluation

The esophageal functional tests were performed during any time of the post-transplant period according to clinical suspicion for GERD diagnosis, mostly by dyspeptic symptoms or decline >10% of forced expiratory volume in the first second (FEV1). All included patients had the following tests performed: contrast radiography of the esophagus, stomach, and duodenum, upper digestive endoscopy, esophageal manometry, and 2-channel, 24-hour pH monitoring (computerized device Multiplex II, Alacer Biomedica). Diagnosis of pathological GERD was made on the basis of (1) deMeester index >25 or (2) erosive esophagitis grade 3 or 4 from the Los Angeles Classification System. We ruled out pathological GERD when deMeester index was <10 and erosive esophagitis was absent.

RESULTS

Of 168 lung transplantations performed between January 2003 and June 2015, we included in the preliminary analysis the first 6 patients evaluated, divided into 2 groups according to GERD and CLAD status: (1) 4 patients with

Table 2. Clinical Characteristics and Outcomes of Group 3: Patients With Evidence of Foreign Body on Lung Biopsy

| | Age (y) | Type of Procedure | Lung Disease | ACR (n) | NB | Other Pathological Findings | Outcome | BAL Neutrophils | BAL Culture |
|--------|---------|-------------------|-----------------|---------|-----|-----------------------------|--------------------------------|-----------------|-------------|
| Case 1 | 38 | Bilateral | Bronchiectasis | 1 | Yes | Chronic bronchiolitis | CLAD and Re-transplant (86 mo) | 20% | Negative |
| Case 2 | 40 | Bilateral | Cystic fibrosis | 0 | No | None | CLAD absent (21 mo) | 10% | Negative |
| Case 3 | 26 | Bilateral | Bronchiectasis | 0 | No | None | CLAD absent (35 mo) | 10% | Negative |
| Case 4 | 43 | Bilateral | Bronchiectasis | 0 | No | None | CLAD absent (14 mo) | 5% | Negative |
| Case 5 | 21 | Bilateral | Cystic fibrosis | 0 | No | None | CLAD absent (39 mo) | 10% | Negative |

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