COMP: A Potential Early Biomarker of RAS After Lung Transplantation

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Background. Chronic rejection, defined as chronic lung allograft dysfunction (CLAD), is the major factor limiting long-term survival after lung transplantation (LTx). A specific subgroup of CLAD is restrictive allograft syndrome (RAS). CLAD’s pathogenesis is largely unknown, but previous findings suggest that it is associated with increased fibrosis in the transplanted lung. Cartilage oligomeric matrix protein (COMP) has been associated with multiple fibrotic conditions. The current study aimed to explore the relation between COMP serum levels and development of CLAD, and RAS in particular, in a retrospective cohort of LTx patients. Methods. This study included retrospective data from patients who underwent LTx during 2009–2011. Blood samples and spirometry data were obtained at follow-up visits 1, 3, 6, 9, and 12 mo after transplantation. Serum samples were analyzed for COMP. CLAD and RAS were defined according to the 2019 International Society for Heart and Lung Transplantation consensus document. Results. Data from 38 patients (19 men and women, respectively) were collected. Twenty-three patients (60.5%) developed CLAD, of whom 6 (26.1%) fulfilled the criteria for RAS. Patients who developed RAS had higher mean COMP levels between 1 and 3 mo after LTx than those who did not develop RAS (10.9 [3.9–17.5] U/L vs 7.4 [3.9–10.8] U/L, P = 0.008). RAS was also associated with shorter survival. We found no association between COMP levels and CLAD of other types than RAS. Conclusions. Serum level of COMP early after LTx seems to be associated with RAS development and might serve as a biomarker suitable for clinical use in the LTx setting.

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INTRODUCTION

Lung transplantation (LTx) is a potentially life-saving procedure for patients with end-stage lung disease in otherwise good health. According to the International Society for Heart and Lung Transplantation (ISHLT), the most common indications for LTx are interstitial lung disease/pulmonary fibrosis (PF)—32%, chronic obstructive pulmonary disease—30%, and cystic fibrosis—15%. However, long-term survival is limited. Adults with a primary lung transplant currently have a median survival of 6.7 y.1 Chronic rejection is the most important factor limiting long-term survival after lung transplantation. Historically chronic rejection has been equal to bronchiolitis obliterans syndrome (BOS). However, it was recently redefined into chronic lung allograft dysfunction (CLAD).2 CLAD is described as the presence of an irreversible decline of forced expiratory volume 1 s (FEV1) to ≤80% of a baseline FEV1, which is similar to the definition of BOS. A specific subgroup of CLAD, called restrictive allograft syndrome (RAS), has also been established. RAS is defined by a restrictive impairment of the lung function in which in addition to the >20% decline in FEV1 from baseline, there is a concomitant >10% decline in total lung capacity, in sample collection and study performance and writing of the article. A.J.B. participated in laboratory analysis and data analysis. R.N. participated in research design, data analysis, and writing of the article. J.M. participated in research design, sample collection, data collection, data analysis, and writing of the article. All authors read and approved the final version of the article. Correspondence: Mirza Novo, MD, Department of Internal Medicine/Respiratory Medicine and Allergology, Institute of Medicine, University of Gothenburg, Bruna stråket 11, SE-413 46 Gothenburg, Sweden. Copyright © 2021 The Author(s). Transplantation Direct. Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal. ISSN: 2373-8731 DOI: 10.1097/TXD.000000000001189

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CLAD’s pathogenesis remains unclear, although repeated injury to the allograft by ischemia-reperfusion, acute rejection, inflammation, alloreactivity directed toward HLA antigens and infections, cytomegalovirus (CMV) infection, has been reported to contribute to CLAD development.5 Several biomarkers have been associated with CLAD’s prediction and development, but data are inconsistent.5

The underlying pathology of obstructive CLAD is considered to be bronchiolitis obliterans, with an excess of subepithelial fibrous tissue in the early phase and obliteration of the lumen by fibrosis in a later phase.2 RAS, on the other hand, exhibits characteristic radiological findings—multilobular ground-glass opacities primary in the upper lobes and often pleural fibrosis. The opacities refer to parenchymal/pleural thickening consistent with a diagnosis of pulmonary or pleural fibrosis and cause restrictive physiology. Histologically, the RAS’s main distinctive feature appears to be a more intraalveolar fibroelastosis adjacent to the bronchioles, pleura, and the interlobular septa.3

Cartilage oligomeric matrix protein (COMP) is a large pentameric glycoprotein that interacts with extracellular matrix (ECM) in various organs and tissues such as cartilage and fibroblasts, vascular smooth muscle cells, cardiomyocytes, and activated platelets.8 It has been shown to stimulate chondrocyte proliferation and chondrogenesis,7,8 to enhance coagulation by activation, aggregation, and adhesion of platelets, and is more abundant in weight-bearing tendons, indicating that COMP may enhance the strength of the ECM.9 Studies have suggested an important role of COMP in a range of malignant conditions such as breast cancer,10 prostate cancer,11 and colon cancer,12 as well as chronic hepatitis C.13 Thus, COMP has been proposed as an early predictive biomarker of several diseases.14,15

Because COMP levels have been associated with multiple fibrotic conditions and previous findings suggest that CLAD and especially RAS is associated with increased fibroproliferation,3 the current study aimed to examine the potential presence of an association between COMP levels in serum and the development of CLAD/RAS in longitudinal serum samples from a retrospective cohort.

MATERIALS AND METHODS

Adult patients who underwent LTx at Sahlgrenska University Hospital, Gothenburg, Sweden, were previously included in a prospective longitudinal study between February 2009 to April 2012.16 From this cohort, 38 patients with possible pairwise CLAD/non-CLAD, based on clinical diagnosis, were selected, matching for sex, age, and pretransplant diagnosis. If an optimal match was not available, sex was prioritized, then the diagnosis, and finally, age. The matching was performed before the end of follow-up. Variables were mainly retrieved from the existing database, and to some extent, the patients’ medical records. Variables recorded were recipient sex, age at transplantation, underlying disease, transplant type, CLAD development, death, age at death, and survival time. Respective treating physician had defined CLAD at the time of patient selection. Due to an unplanned delay in sample analysis, the follow-up was longer than initially planned.

Furthermore, at the end of the main study, all patients’ static and dynamic spirometries and imaging and medical records were reviewed independently by 2 experienced pulmonologists, and all discrepancies were resolved by consensus. All CLAD diagnoses in the current material were revisited after the publication of the 2019 ISHLT guidelines.5 Clinical data were collected retrospectively from patient charts, and the last follow-up of clinical data was made in February 2020. The study was approved by the regional ethical review board in Gothenburg (Dnr791-08), and all subjects provided written and verbal informed consent.

All patients received antithymocyte induction therapy, and the immunosuppression was a combination of a calcineurin inhibitor, either cyclosporin or tacrolimus, with mycophenolate and prednisone. The calcineurin inhibitor and prednisone dose were tapered at 3, 6, and 12 mo per protocol, while the mycophenolate dose was kept relatively unchanged. Three different clinical stages were defined according to the degree or intensity of immunosuppressive therapy: 1–3 mo (M3), 4–6 mo (M6), and 7–12 mo (M12) after LTx.

A comprehensive retrospective review was performed of patient laboratory charts to identify possible differential counts for blood eosinophils. In parallel, all available BAL pathology reports from all included patients were reviewed for differential counts with the presence or absence of eosinophils clearly described. No further analysis was performed based on the blood eosinophils. The BALs were associated with the clinical stage in closest proximity to when the bronchoscopy was performed and grouped based on eosinophilia. Eosinophilia in BAL was defined as ≥2% eosinophils in the differential count.17

According to the protocol of the main study, serum samples and spirometry data were collected at follow-up visits at 1, 3, 4.5, 6, 9, and 12 mo after transplantation. All available serum samples collected during the first year after transplantation were analyzed for COMP. The mean serum levels of COMP according to the different clinical stages of immunosuppressive therapy were calculated. CLAD2 and RAS3 were defined according to the 2019 ISHLT consensus documents.

Stored (−80°C) serum samples were thawed and analyzed for COMP using a commercial ELISA test (ImmunoDiagnostic Systems, Boldon, United Kingdom) according to the manufacturer’s instructions. Briefly, 20 µL of serum was diluted with 180 µL sample buffer and added in duplicates to a 96-well plate, and incubated on a shaker at 250 rpm with anti-COMP antibodies for 120 min at room temperature. Thereafter, the reporter substrate was added, and the plate was incubated for 15 min. Subsequently, the plate was analyzed at 450 nm, and the reference background was determined at 650 nm. A reference sample of known concentration was applied to generate a standard curve.

Comparisons on group level for numerical variables were performed using the Mann–Whitney U test and Fisher exact test for categorical variables. A P value <0.05 was considered significant. GraphPad Prism version 9.0.1 for Mac, GraphPad Software, (San Diego, CA) was used for all statistical analyses.

RESULTS

Thirty-eight patients (19 each female/male) were included (Table 1). The mean age at the time of transplantation was 56.12 (range 31–73) y. Most of the patients were transplanted...
because of PF (42.1%) and chronic obstructive pulmonary disease (39.5%). Double lung transplant was most common (65.8%). Twenty-three patients (60.5%) developed CLAD, of whom 6 (15.8%) developed RAS until the last date of follow-up. The remaining 17 patients were defined as having a BOS phenotype. During the study period, 52.6% (n=20) of the patients died, and the mean observed survival time was 6.2 y (range 0.9–10.5). The median time to CLAD was 29 mo (range 8–96). The median time to RAS was 10 mo (range 8–36).

We did not find any significant difference in levels of COMP at M3, M6, and M12 between patients who developed CLAD and those who did not (Figure 1). Further analysis of the RAS subgroup revealed that the mean levels of COMP during M3 were significantly higher among those who developed RAS than those who did not develop RAS (10.9 [8.2-17.5] U/L versus 7.4 [3.9-10.8] U/L, P=0.008; Figure 2). Moreover, the levels of COMP among those with RAS were slightly higher also during M6, although not statistically significant.

A separate analysis of RAS patients (Table 2) was performed. We did not find any significant difference regarding mean age at the time of transplantation between those with RAS versus No-RAS (60.5 [42-70] versus 55.6 [31-73]) y; P=0.199). The RAS patients were mainly (66.7%) operated with single LTx compared with 28.1% among the No-RAS patients. Transplant type and PF were, therefore, identified as potential confounders. However, there were no statistically significant differences in COMP levels if grouped on Single versus Double LTx nor if grouped on PF versus no PF as transplant diagnosis. We also found that patients with RAS had significantly shorter mean survival time compared with those without (2.4 [0.9-9.0] versus 6.9 [1.4-10.5] y, P=0.002).

In the retrospective analysis of laboratory charts, only 5 blood differential counts were found, and one of these showed eosinophilia. In the retrospective analysis of BAL cytology, 83 counts of full differential counts were recorded. The pooled analysis of COMP levels and BAL samples showed that the COMP levels were significantly higher (P=0.0246) among the samples collected in the proximity of BAL with eosinophilia than those without (Figure 3).

**DISCUSSION**

This study shows that the mean increase in COMP serum levels between the 1- and the 3-mo control after LTx was significantly elevated in patients who later developed RAS, than in patients who did not develop this complication. As expected, we found that RAS was associated with shorter survival after lung transplantation in our cohort. To our knowledge, this is the first time COMP levels have been associated with RAS development.

CLAD’s mechanism and its different phenotypes are still uncertain and poorly understood. However, fibroproliferative processes are a distinct pattern in both phenotypes.

Fibrosis is a process characterized by excess ECM. COMP has displayed an important role in the deposition of type I collagen, which leads to the activation and conversion of fibroblasts to myofibroblasts and takes place following infiltration of inflammatory cells with or without an excessive mechanical stretch of these tissues.

Like IPF, the RAS phenotype of CLAD shows a pattern of fibroelastosis, suggesting a possible rationale for the association of elevated COMP in serum and RAS. Epithelial to mesenchymal transition has been suggested as the key mechanism in CLAD development. TGF-β plays a central role in the development of epithelial to mesenchymal transition, and COMP catalyzes the fibril formation by promoting the early association of collagen molecules, leading to an increased fibrillogenesis and a more distinct organization of the fibrils.

The Leuven group showed an inferior survival among RAS patients with elevated eosinophils in blood and elevated neutrophils in bronchoalveolar lavage (BAL), suggesting a possible association of eosinophilic inflammation with RAS. Neutrophils act as direct modulatory cells in fibroblast proliferation, collagen synthesis, and lattice contraction, in part, through TGF-β. Our finding that serum levels of COMP were elevated already at month 3 posttransplant suggests that the detrimental process eventually resulting in RAS development may start already at a very early time-point during the posttransplant period. That this association is only found in the first samples could suggest that the mechanisms for RAS promotion change over time. An association between COMP and eosinophils has been shown in cartilage degradation. These findings could suggest an inflammatory interaction between COMP and eosinophils in lung allograft dysfunction, possibly leading to a rapidly evolving fibrosis in RAS. Our series shows an association between BAL eosinophilia and serum levels of COMP. Although this finding confirms the previous studies of an association between COMP and eosinophils, it also supports the hypothesis that COMP might be associated with the pathophysiological mechanisms behind RAS.

Furthermore, Inui et al demonstrated the pivotal role of COMP and TGF-β in the assembly of collagen V (col(V)) in the extracellular matrix. Previous data have shown that col (V) is a target of the immune response during lung allograft rejection that leads to primary graft dysfunction.

**TABLE 1.**

| Variable                             | n (N = 38)   |
|--------------------------------------|-------------|
| Female                               | 19 (50.0)   |
| Diagnosis                            |             |
| Alpha-1 trypsin deficiency           | 4 (10.5)    |
| Alveolar macrothiliasis              | 1 (2.6)     |
| COPD                                 | 15 (39.5)   |
| Pulmonary fibrosis                   | 16 (42.1)   |
| Sarcoidosis                          | 1 (2.6)     |
| Scleroderma                          | 1 (2.1)     |
| Transplant type                      |             |
| Single                               | 13 (34.2)   |
| Bilateral                            | 25 (65.8)   |
| Chronic Rejection                    |             |
| None                                 | 15 (39.5)   |
| CLAD                                 | 23 (60.5)   |
| BOS                                  | 17 (44.7)   |
| RAS                                  | 6 (15.8)    |
| Death at end of follow-up            | 20 (52.6)   |
| Mean                                 |             |
| Age at time of LTx, y                | 56.12       |
| Survival, y                          | 6.2         |

BOS, bronchiolitis obliterator syndrome; CLAD, chronic lung allograft dysfunction; COPD, chronic obstructive pulmonary disease; LTx, lung transplantation; RAS, restrictive allograft syndrome.
graft dysfunction is an important independent risk factor for the development of BOS.\textsuperscript{29,30} Col (V) is overexpressed in lung biopsies of BOS patients, and the alfa1 (V)-specific antibody is detected in bronchoalveolar lavage fluid of lung transplant patients.\textsuperscript{31} Thus, COMP, TGF-beta, col (V), and eosinophils, could, through mutual influence, contribute to fibrosis development, which is shown to be one of the most important processes in the development of CLAD and RAS.\textsuperscript{3} COMP may have an initializing role in this process.

In our study, two-thirds of RAS patients received single lung transplantation (SLTx) compared with one-third among no-RAS. Moreover, half of the RAS patients were IPF patients, which has previously been associated with a higher risk for RAS\textsuperscript{32} and elevated levels of COMP.\textsuperscript{33} However, there were no statistically significant differences in relation to SLTx nor IPF between the RAS and the No-RAS populations. Furthermore, there was no significant association between either factor or COMP. We, therefore, deem it unlikely that either factor is confounding the results. There are, to the best of our knowledge, currently no normal values of COMP in sera of healthy adults to compare our results with. In a small population of healthy adults, the mean serum COMP concentration of 9.98 ± 3.38 U/l has been reported.\textsuperscript{34}

However, the current study has several limitations. As a single-center retrospective cohort study at a specialty referral center affiliated with an academic tertiary referral center, restricting its applicability to the general population. Moreover, the retrospective design can generate hidden and
TABLE 2
Characteristics of the patients that developed restrictive allograft syndrome RAS

| Variable                        | RAS (n = 6) | No-RAS (n = 32) | P     |
|---------------------------------|------------|----------------|-------|
| Female                          | 3  (50.0)  | 16  (50.0)     | 0.67  |
| Diagnosis                       |            |                |       |
| Alpha-1 trypsin deficiency      | 2  (33.3)  | 2   (6.3)      | 0.1   |
| Alveolar microlithiasis         | 0          | 1   (3.1)      | 0.8   |
| COPD                            | 1  (16.7)  | 14  (43.8)     | 0.22  |
| Pulmonary fibrosis              | 3  (50.0)  | 13  (40.6)     | 0.52  |
| Sarcoïdosis                     | 0          | 1   (3.1)      | 0.8   |
| Scleroderma                     | 0          | 1   (3.1)      | 0.8   |
| Transplant type                 |            |                |       |
| Single                          | 4  (66.7)  | 9   (28.1)     | 0.09  |
| Bilateral                       | 2  (33.3)  | 23  (71.9)     | 0.199 |

| Variable                        | Mean       | Range     | Mean       | Range     | P     |
|---------------------------------|------------|-----------|------------|-----------|-------|
| Age at time of LTx, y           | 60.5       | 42–70     | 55.6       | 31–73     | 0.199 |
| Survival, y                     | 2.4        | 0.9–9.0   | 6.9        | 1.4–10.5  | 0.002 |

COPD, chronic obstructive pulmonary disease; LTx, lung transplantation; RAS, restrictive allograft syndrome.

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