Review Article

J Korean Soc Transplant 2016;30:120-124
http://dx.doi.org/10.4285/jkstn.2016.30.3.120

JKST

Chronic Rejection after Lung Transplantation

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A new classification system for chronic rejection in lung transplantation was recently proposed. Chronic lung allograft dysfunction (CLAD) is regarded as chronic rejection after excluding other causes of allograft dysfunction. CLAD is divided into obstructive CLAD (bronchiolitis obliterans syndrome) and restrictive CLAD (restrictive allograft syndrome). In this review, we will review the latest concepts and current controversies regarding the new CLAD terminology, diagnostic approach, risk factors and possible treatment options.

Key Words: Lung transplantation, Graft rejection, Bronchiolitis obliterans
중심 단어: 폐이식, 이식편거부반응, 폐쇄성 세기관지염

INTRODUCTION

The number of lung transplantation (LTx) is recently increasing, however, the rate of long-term survival after LTx remains low. According to the recent report of International Society for Heart and Lung Transplantation (ISHLT), 5-year survival is only about 55%(1). Chronic rejection is one of the major problem hindering long-term survival in patients with LTx and more than 50% patients at 5-year posttransplant develop chronic rejection(1).

Originally, pathological obliterative bronchiolitis (OB) was regarded as chronic rejection(2,3). However, it is difficult to prove on small biopsies. As a result, the term bronchiolitis obliterans syndrome (BOS) was adopted to explain syndrome of late-onset and chronic decline of allograft function (>20% decline in forced expiratory volume in 1s, FEV_1, compared to the best postoperative baseline). BOS or OB was considered the equivalent to chronic rejection(4). However, some LTx patients may develop a restrictive pattern of allograft dysfunction which is different from BOS(5,6). This syndrome was defined as restrictive allograft syndrome (RAS)(6,7). In this review, we will review about chronic rejection based on these new insights and paradigm shifts.

Received September 9, 2016
Accepted September 9, 2016

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1. Chronic lung allograft dysfunction (CLAD)

Recently, a new classification system for chronic rejection was proposed(8). CLAD is regarded as chronic rejection after excluding other causes of allograft dysfunction. CLAD is defined as a persistent (for at least 3 weeks) decline of FEV_1 and/or forced vital capacity (FVC) of at least 20% in comparison with the baseline, which is considered as the mean value of the two best posttransplant measurements with at least 3 weeks interval(8).

CLAD is not the term of diagnosis but the status of persistent decline compared to the best posttransplant lung function values. Therefore, every possible causes of persistent decreased function should be ruled out. When other specific causes are excluded (Table 1), the graft dysfunction can be explained by CLAD.

After excluding other causes leading to the decline of al-

lograft function, further work-up is needed. Work-up generally include thorax computed tomography (CT) with both insipiratory and expiratory phase, full pulmonary function test (PFT), and bronchoscopy with transbronchial biopsies (TBLB), bronchoalveolar lavage (BAL) with cultures and total and differential cell count. The phenotype of CLAD can be classified based on the results of work-up.

1) Bronchiolitis obliterans syndrome (BOS)

OB has been the hallmark of chronic rejection since 1984, at which Burke et al. describe that term(2). OB is a fibroproliferative obliteration in the small airway and it is difficult to prove by TBLB due to low sensitivity(2,3,9). As a result, expert group in ISHLT suggested concept of BOS as the clinical term correlated with OB(4). The definition of BOS was a persistent, progressive and irreversible decline of FEV_1 with airway obstructive pattern and the category was divided to 4 groups based on FEV_1 decline in comparison with the baseline, which is considered as the mean value of the two best posttransplant measurements with at least 3 weeks interval(4). At first update about BOS definition, one more category was added, that was BOS 0-p (potential BOS), which further included values of forced expiratory flow at 25 and 75% of vital capacity ($FEF_{25\sim75\%}$). And definition of staging system proposed in this statement was shown in Table 2(10). Second revision about BOS approved by ISHLT was recently published. It updated the pathophysiology of BOS and strategies to manage patients with BOS(11).

Various risk factors for BOS has been suggested(11, Table 3) Among them, the role of antibody-mediated rejection with the development of donor-specific antibodies (DSA) has been identified recently. Recipients with early or late development of DSA and persistent DSA tend to easily develop to BOS(12-14). And the role of non-HLA antibodies to self- antigens (collagen V and K-α1 tubulin) has been suggested(15).

Table 1. Confounding factors leading to FEV_1 decline other than chronic rejection

Allograft-related
Persistent acute rejection
ARAD
Infection/Colonization
Anastomotic stricture
Disease recurrence
Follicular bronchiolitis
Extra-allograft
Pleural disease
Diaphragm dysfunction
Native lung hyperinflation
Other causes

Abbreviations: ARAD, azithromycin-responsive allograft dysfunction.
Adapted from Fig. 1 of reference [8].

Table 3. Risk factors for BOS

Primary graft dysfunction
Acute cellular rejection
Lymphocytic bronchiolitis
Antibody-mediated rejection (*de novo* donor-specific anti-human leukocyte antigen antibodies)
Gastroesophageal reflux and microaspiration
Introduction/Colonization
Persistent neutrophil reflux and sequestration
Autoimmunity (e.g. collagen V sensitization)
Air pollution
Genetic factors

Abbreviations: BOS, bronchiolitis obliterans syndrome.
Adapted from Table 1 of reference [11].

Table 2. Original and proposed classification of BOS

Original classification		Current proposition	
BOS 0	FEV_1 80% or more of baseline	BOS 0	FEV_1 > 90% of baseline and $FEF_{25\sim75\%}$ of baseline
		BOS 0-p	FEV_1 81% to 90% of baseline and/or $FEF_{25\sim75\%}$ < 75% of baseline
BOS 1	FEV_1 66% to 80% of baseline	BOS 1	FEV_1 66% to 80% of baseline
BOS 2	FEV_1 51% to 65% of baseline	BOS 2	FEV_1 51% to 65% of baseline
BOS 3	FEV_1 50% or less of baseline	BOS 3	FEV_1 50% or less of baseline

Abbreviations: BOS, bronchiolitis obliterans syndrome; $FEF_{25\sim75\%}$, mild-expiratory flow rate; FEV_1, forced expiratory volume in 1 second.
Adapted from Table 1 of reference [10].

The treatment of BOS is still difficult due to the unclarity of pathophysiology and causes. However, several treatment has been tried although most modalities have shown minimal success rate. It was switching immunosuppressive agents, addition of montelukast, cyclophosphamide, methotrexate, total lymphoid irradiation and extracorporeal photopheresis(16). Recently, fundoplication can be performed when gastroesophageal reflux is diagnosed in BOS patients(11). Additionally, azithromycin can be potentially beneficial in BOS, and there are many reports about that. There is report that about 40% of BOS patients can respond to azithromycin(17). BAL neutrophilia (>15%) was suggested as predictive marker of responsiveness to azithromycin, however this is controversial due to neutrophilia can be shown due to coexistent infection(18-22). Responders to azithromycin which is defined as a FEV_1 increase of ≥10% after a 2~3 month treatment were initially categorized as neutrophil-reversible allograft dysfunction (NRAD), but renaming as azithromycin - responsive allograft dysfunction (ARAD) was recently suggested(11,23). Considering the definition of CLAD, ARAD may be a potential confounder of BOS. Therefore, it is advised to take azithromycin for about 3 months in all patients with decline of lung function consistent with CLAD/BOS(8,11). Finally, retransplantation can be performed in well selected patients for only curative purpose of BOS(11,24).

2) Restrictive CLAD (rCLAD): restrictive allograft syndrome (RAS)

Recently, several groups reported about the existence of a restrictive phenotype of CLAD (rCLAD). There is no international and consistent definition for rCLAD, however, several groups suggested the different diagnostic criteria. Woodrow et al. divided CLAD patients to restrictive CLAD (FVC decline ≥20%) with pleuroparenchymal infiltrates on CT and obstructive CLAD (FVC decline <20%)(25). Sato et al. suggested the concept of RAS which is a group of patients with restrictive PFT decline (a decline in TLC of ≥10% compared to the best posttransplant baseline and with a decline in FEV_1 ≥20%)(6). This definition has several problems including not applying to single lung transplant and not performing TLC routinely. Other group used the ratio of FEV_1/FVC ratio in defining rCLAD, and this definition has problem of normal or increased FEV_1/FVC if FVC and FEV_1 simultaneously is decreased(26). Todd et al conducted a study using spirometry alone to diagnose rCLAD(27). They divided CLAD as restrictive (FVC/FVC_{best} <0.80) and obstructive (FVC/FVC_{best} ≥0.80) CLAD.

CT scan can be useful for diagnosing rCLAD. CT scan in rCLAD showed persistent infiltration, volume loss and hilus retraction to pleuroparenchymal fibro-elastosis(7). Biopsy findings also can help to diagnose patients with rCLAD. One recent study showed that acute fibrinoid-organizing pneumonia (AFOP) was diagnosed on TBLB biopsies with FEV_1 decrease ≥20% and FEV_1/FVC >0.70(28).

Taken together, there are different approaches in diagnosing rCLAD. A multimodal approach, using functional (i.e. lung function), radiologic and histopathologic evaluation of the allograft is needed to diagnose rCLAD.

The prevalence of rCLAD is presumed about 30-35% based on several reports(6,25-27). And several reports showed that the survival rate after diagnosis of rCLAD was shorter than of BOS (0.8~1.5 years vs. 3~4 years)(6,25-27). However, further multicentric and prospective studies are needed to confirm the poor outcome of rCLAD compared to the patients with BOS.

There are some reports about risk factors for the development of rCLAD. Those are severe lymphocytic bronchiolitis, late-onset diffuse alveolar damage, BAL eosinophilia, increased BAL protein levels of alarmins, diagnosis of sarcoidosis or interstitial lung diseases before transplantation, younger age, female gender, CMV donor/recipient mismatch and other risk factors which are common in BOS(29-32). However, those risk factors were derived from small studies and were not applied to other groups with rCLAD. Therefore, the significance of reported risk factors for development of rCLAD is still speculative.

The treatment of rCLAD remains unknown. The same therapeutic options for BOS are usually been tried, however, the most options showed the fail. There are some reports about possible improvement with pirfenidone, an antifibrotic agent, recently used for the treatment of IPF, or alemtuzumab (Campatho-1H), an antagonist of CD52, which showed the interstitial changes and lung function in small group with rCLAD (33,34). Several centers reported that patients with rCLAD were likely to have DSA more frequently(35),

which may be the key of new treatment options. Further larger and multi-center study will be necessary to find a possible management. And unfortunately, the results of re-transplantation in patients with rCLAD are much worse than with BOS, therefore, strict selection criteria for re-transplantation for rCLAD should be applied(36).

Conclusion

In summary, CLAD was recently suggested concept including different phenotypes of BOS and rCLAD (RAS). Different pathophysiological mechanisms may be involved these distinct phenotypes, because histology, allograft function and imaging are different. However, at present, we don't know about definite pathophysiology, risk factors and treatment. Future research on pathophysiology, mechanisms and natural history is needed, only by doing we can understand the basis for development of therapeutic options. This is the hope for LTx patients to live long overcoming CLAD.

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