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Research paper

CT at onset of chronic lung allograft dysfunction in lung transplant patients predicts development of the restrictive phenotype and survival

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ABSTRACT

Purpose: To describe early signs for restrictive subtype of chronic lung allograft dysfunction (CLAD) after lung transplantation in computed tomography (CT) and to evaluate the predictive value for disease progression and survival.

Material and methods: 52 CT examinations in lung transplant patients at CLAD onset were scored for CT features referring to airways disease, parenchymal or pleural abnormality. Patients with and without later development of restrictive CLAD (TLC ≤ 80%) were compared. A radiological score for inflammation including pleural effusion, central and peripheral ground glass opacities and consolidations was calculated and used for survival analysis.

Results: CT of patients with later development of restrictive CLAD showed significantly more often abnormalities at CLAD onset, in particular consolidations (57% vs. 4%; $p < 0.001$) and ground glass attenuations (71% vs. 7%; $p < 0.001$) than those of patients without the restrictive phenotype. CT score for inflammation was significantly higher in patients with than without later restrictive CLAD (3.4 vs. 0.6; $p < 0.001$). Survival of patients with a high score (> 2) for inflammation in CT at CLAD onset was significantly lower than of those with a low score (443 vs. 2415 days; $p = 0.019$).

Conclusions: CT at CLAD onset differs in patients with/without later development of the restrictive phenotype. It is therefore an indicator for future development of restrictive CLAD and predictor for survival. It should be implemented in the diagnostic work-up at diagnosis of CLAD.

1. Introduction

Lung transplantation is an established treatment method for patients with end-stage pulmonary diseases [1]. Chronic lung allograft dysfunction (CLAD) is the main life limiting factor after lung transplantation [2]. For years, bronchiolitis obliterans syndrome (BOS) was considered the pathological correlate of CLAD until other phenotypes were recently described.

The clinical diagnosis of BOS is based on a decline of the forced expiratory flow in one second (FEV_1) by at least 20% compared to the postoperative baseline value (BL) with no other possible cause [3,4]. CT findings of BOS include air-trapping and bronchial wall thickening [5,6]. Bronchiectasis, mucus plugging and consolidations have also been described [6–9].

The other phenotypes of CLAD that have recently been identified include the restrictive phenotype (restrictive CLAD) and the neutrophilic reversible allograft dysfunction (NRAD) [10–12]. Patients with restrictive CLAD present with a restrictive pulmonary function

Abbreviations: BAL, bronchoalveolar lavage; BL, baseline; BOS, bronchiolitis obliterans syndrome; CI, confidence interval; CLAD, chronic lung allograft dysfunction; CT, computed tomography; FEV_1, forced expiratory flow in one second; FVC, forced expiratory volume; IQR, interquartile range; ISHLT, International Society for Heart and Lung Transplantation; LTx, lung transplantation; NRAD, neutrophilic reversible allograft dysfunction; PFT, pulmonary function tests; RAS, restrictive allograft syndrome; SLTx, single lung transplantation; TLC, total lung capacity

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deficit and fibrotic changes on CT [12–14]. The definition of restrictive CLAD varies in the literature [14–17]. While Sato reports decline in total lung capacity (TLC) below 90% of the BL [12] as important clinical outcome parameter, Woodrow defined the reduction of forced expiratory volume (FVC) under 80% of the best FVC at the time of CLAD onset as prognostic threshold [15]. Suhling showed significant effects for TLC decline ≤80% of the BL after CLAD onset and integrated post CLAD interstitial changes in diagnosis of restrictive CLAD [14].

Restrictive CLAD affects approximately 5–30% of CLAD patients depending on definition. The patients with restrictive CLAD have a poor prognosis [12]. In CT, patchy or diffuse ground-glass opacities with occasional consolidation followed by progression of consolidation, interstitial reticular shadows and traction bronchiectasis have been described as characteristic patterns in patients with restrictive CLAD [18]. Similar results were reported by Verleden with ground glass opacities and septal and non-septal lines at CLAD onset and bronchiectasis, consolidations, architectural distortion, volume loss and hilum retraction as late findings after CLAD onset [19].

The aim of our study was to find early signs for restrictive CLAD which indicate its development before a restrictive lung function becomes apparent. Imaging patterns in CT at CLAD onset were evaluated and compared between patients with and without development of restrictive CLAD in the further course. Further on, the predictive value of CT at CLAD onset and a CT-based score on disease course and patient survival was evaluated.

2. Material and methods

2.1. Study design

This is a retrospective single centre study which has been approved by the Internal Review Board (No. 2676-2015). 1191 patients who underwent bilateral lung transplantation or heart-lung transplantation between 9/1987 and 6/2012 were screened for development of CLAD according to the guidelines of the International Society of Heart and Lung Transplantation [4]. All patients with CLAD (n = 462) aged ≥18 years and with at least one CT examination at CLAD onset (within ± 100 days of diagnosis of CLAD) were included (n = 52). Patients with bronchial anastomotic stenosis, malignancy, acute infection, acute rejection, pneumothorax or intubation at the time of CT were excluded (Fig. 1). Patients were divided into two groups, those with TLC loss over time (TLC ≤ 80%, restrictive CLAD) and those without. The average follow-up period was 5.9 years (IQR 3.7–9.5) after transplantation and 3.4 years (IQR 1.7–4.4) after CLAD onset.

2.2. Pulmonary function tests

All patients underwent body plethysmography measurement at least four times in the first year after lung transplantation (LTx), twice in the second and annually from beginning of 3rd year. Additional spirometry was performed when indicated, all lung function measurements were performed according to the guidelines of the European Respiratory society [20]. CLAD was diagnosed according to the guidelines of the International Society of Heart and Lung Transplantation (ISHLT) when FEV_1 decreased of at least 20% of the postoperative baseline value unexplained by acute rejection, infection or other complications [4]. The severity of BOS is graded according to the degree of obstruction found in pulmonary function tests (PFT): BOS 1 describes a 20–34% decrease in FEV1 from baseline; BOS 2 a 35–49% decrease in FEV1; and BOS 3 at least a 50% decrease in FEV1 from baseline [4]. Patients were screened for restrictive CLAD using a TLC threshold of TLC ≤ 80% of the BL [14]. The BL was defined as the mean of the two best TLC values. The last TLC-value determined restriction when measured repeatedly under threshold.

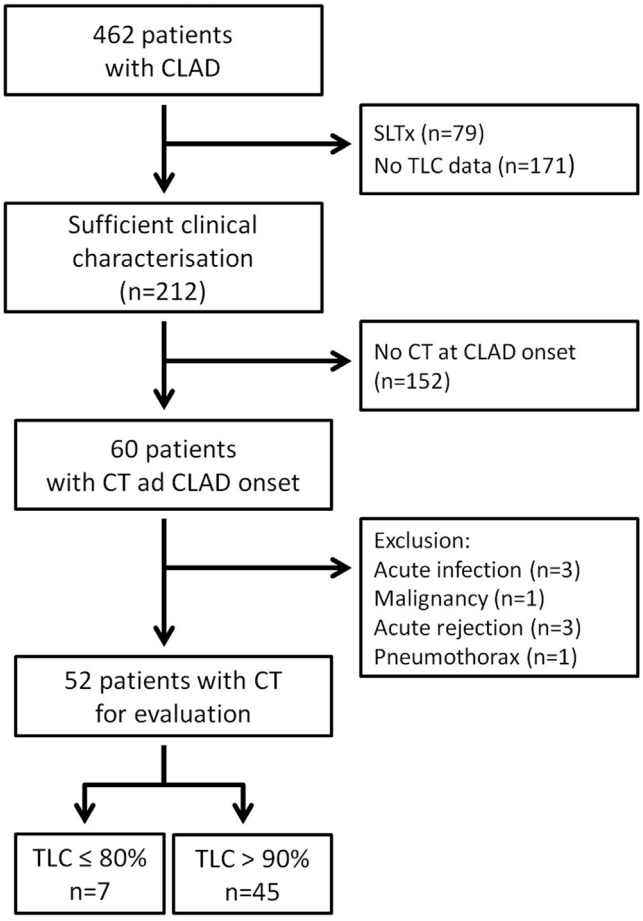

Fig. 1. Flow chart of inclusion. CLAD = chronic lung allograft dysfunction; SLTx = single lung transplantation; TLC = total lung capacity.

2.3. Bronchoalveolar lavage

Surveillance bronchoscopy with bronchoalveolar lavage (BAL) and transbronchial biopsies were performed at 1, 3, 6 and 12 months after transplantation and additionally when unexplained deterioration of graft function occurred. Results from BAL were evaluated for neutrophilia, eosinophilia and lymphocytosis.

2.4. CT data acquisition

CT-examinations were performed at our local radiology department or externally. Local CT examinations were obtained with a 64 row MDCT (Lightspeed VCT, GE healthcare, Milwaukee, United States) or a 16 row MDCT (Lightspeed 16, GE healthcare, Milwaukee, United States). All CT data were acquired volumetrically using a standard dose protocol with 120 kV and 100 mAs. CT data were reconstructed with a slice collimation of 1.25 mm and an interval of 1 mm using a “standard” reconstruction kernel for soft tissue and a “lung” reconstruction kernel. The field of view was adapted according to the size of the patients’ lung. External CT examinations (n = 27) were performed with differing protocols and a slice thickness varying from 1.25 mm to 5 mm. CTs with insufficient quality due to a slice thickness > 5 mm or severe motion artefacts were excluded. Additional expiratory scans were performed in 32 cases.

CT examinations within ± 100 days of diagnosis of CLAD were evaluated. If several CT examinations were obtained in one patient the CT examination with the shortest interval to the CLAD onset was selected.