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Functional and computed tomographic evolution and survival of restrictive allograft syndrome after lung transplantation

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BACKGROUND: Restrictive allograft syndrome (RAS) has recently been defined as a novel phenotype of chronic lung allograft dysfunction (CLAD) after lung transplantation. The goal was to describe computed tomographic (CT) changes of RAS patients and to correlate this with spirometry and survival.
METHODS: All 24 established RAS patients at our center were retrospectively included. CT scans from pre-CLAD, CLAD, post-CLAD and late-CLAD subjects were systematically evaluated by a blinded observer using a semi-quantitative scoring system. Changes in CT patterns were correlated with spirometry and survival.
RESULTS: The most prominent CT features at diagnosis of CLAD as compared with pre-CLAD were appearance of central ($p = 0.020$) and peripheral ground glass opacities ($p = 0.052$), as well as septal and non-septal lines ($p = 0.020$). Survival after diagnosis of CLAD was only associated with the absolute value of forced vital capacity (FVC) at diagnosis ($R = 0.46$ and $p = 0.021$), and not with any CT alterations. Evolution of CT abnormalities after diagnosis of CLAD included significant increases in (traction) bronchiectasis ($p < 0.0001$), central ($p = 0.051$) and peripheral ($p = 0.0002$) consolidation, architectural deformation ($p = 0.0002$), volume loss ($p = 0.0004$) and hilus retraction ($p = 0.0036$). The absolute FVC decrease post-CLAD diagnosis correlated with CT alterations.
CONCLUSIONS: In the early stages of RAS, central and peripheral ground glass opacities are the most prominent feature on CT, whereas, in later stages, bronchiectasis, traction, central and peripheral consolidation, architectural deformation, volume loss and hilus retraction are more pronounced. CT changes, however, could not predict survival, whereas FVC at diagnosis of CLAD seems to be the best predictor of survival.
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Lung transplantation is the ultimate treatment for patients with end-stage pulmonary disorders. Survival remains hampered by chronic rejection of which the clinical correlate is bronchiolitis obliterans syndrome (BOS) with 50% of patients with BOS 5 years after transplantation.[1] For over 10 years, BOS has been defined as a persistent, obstructive decline in forced expiratory volume in 1 second (FEV_1) in the absence of confounding factors.[2] However, nowadays the term chronic lung allograft dysfunction (CLAD) seems more appropriate as it has become clear that there are different phenotypes of chronic rejection. First, it was observed that, in 35% of so-called BOS patients, azithromycin could improve FEV_1 by $\geq$ 10%, an entity called neutrophilic

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reversible allograft dysfunction.[3] In their bronchoalveolar lavage, these patients display high neutrophil (> 15%) counts and on computed tomography (CT), these patients show more centrilobular abnormalities and signs of tree-in-bud, which resolve after treatment.[4] Subsequently, attention has shifted to the azithromycin non-responsive CLAD patients. On the one hand, there is a strictly obstructive phenotype with air trapping on expiratory CT and small airway occlusions at pathologic examination (obliterative/constrictive bronchiolitis). This pattern is seen in approximately 45% of all CLAD patients and 70% of all irreversible CLAD patients and is consistent with the definition of BOS. On the other hand, a new phenotype has been defined based on a restrictive pulmonary physiology. The entity is defined by using a decline in total lung capacity (TLC) of at least 10%,[5] or a progressive decrease in FEV_1 and/or FVC with an increasing or stable FEV_1/FVC ratio.[6] This restrictive allograft syndrome (RAS) accounts for approximately 30% of all patients suffering from irreversible CLAD and 20% of all CLAD patients.[5,6] Clinically, RAS patients have a median survival of 8 months (vs 35 months for BOS patients).[6] In this study, we aimed to describe functional and radiologic changes in patients who were diagnosed with CLAD, and who fulfilled the RAS criteria.

Methods

Patients' characteristics

Patients who underwent double-lung or heart–lung transplantation between 2001 and 2012 were retrospectively recruited. All patients provided written informed consent before transplantation. CLAD was defined as a persistent FEV_1 decline of $\geq$ 20% compared with the mean of the two best post-operative values. Subsequently, irreversible CLAD was defined as a lack of improvement in FEV_1 after azithromycin therapy. Within the CLAD patient group, RAS was diagnosed in cases of restrictive pulmonary function, based on a decrease in TLC of $\geq$ 10% when available, or a FEV_1/FVC ratio > 0.70 (with declining FEV_1 and FVC) when TLC was unavailable. For purposes of this study, the CT at clinical diagnosis of CLAD was used as a reference scan (CLAD CT). Pre-CLAD CT was the first CT preceding diagnosis of CLAD. Likewise, the first post-CLAD CT (3 months to 1 year after diagnosis of CLAD) and the last available CT scans during follow-up were scored. We used the term CLAD because not all patients immediately develop the typical restrictive pulmonary function defect and we aimed to describe radiologic changes starting from the moment that FEV_1 consistently remained < 20% of the best post-operative values. Pathology reports were available when patients underwent retransplantation, open lung biopsy or autopsy; typical findings have been presented by Ofek et al, who described extensive alveolar fibrosis and septal thickening, but also obliterative bronchiolitis.[7]

CT protocol

CT examinations were performed on Somatom Sensation 16 or 64 or Definition Flash (Siemens AG, Erlangen Germany) devices or a Philips Brilliance 64 device (Philips Medical Systems, Best, The Netherlands) without intravascular contrast media. One volumetric CT data set of the entire thorax was obtained in suspended deep inspiration in the supine position at 120 kV and 140 mA and reconstructed as 1/0.5 mm axial, 5/5 mm axial and 3/3 mm coronal, displayed in lung and mediastinal window-center settings. Another CT data set was also obtained after breath-hold instruction at end-expiration with the patient supine but in a sequential mode with collimation 2 × 1 mm and a table feed of 30 mm at 120 kV and 150 mA. Reconstructions with 1-mm slice thicknesses were calculated and displayed in lung window-center settings.

CT scoring

All the CT data sets were scored using semi-quantitatively scores based on previous descriptions.[4,8] On inspiratory CT, the severity and extent of bronchus dilation (and presence of traction) in the central and peripheral lung were scored, as was the extent of mucous plugging in large airways, extent of centrilobular nodules including tree-in-bud sign, extent and severity of airway wall thickening, extent of consolidation, extent of ground glass opacities, severity of architectural distortion, volume loss, displacement of the hilum, septal thickening and (sub)pleural thickening. The presence of an apicobasal gradient (apical dominant disease) was recorded. The extent of air trapping was scored on expiratory CT. In general, abnormalities were defined according to the Fleischner Society nomenclature.[9] Bronchus dilation was defined as a bronchus lumen diameter greater than the accompanying pulmonary artery outer diameter, lack of tapering of the bronchus, or bronchi visible in the outer centimeter of the lung. Airway wall thickening was defined as a wall thickness/artery diameter ratio of > 0.2, which was assessed subjectively. Each abnormality was scored in five lung lobes, and per lobe the extent involved with the abnormality was estimated as less than one third, between one third and two-thirds or more than two thirds of the lobar volume, or mild, moderate or severe. To assess severity, this number was translated into percent of lung affected. Lung periphery was defined as the outer one third of the lung. CT data sets were scored by a board-certified chest radiologist (P.D.J.) with > 10 years of experience in reading chest CT scans and for whom the reproducibility for most items has been described previously.[8] CT examinations were scored blinded to the time-point of diagnosis. Both coronal and axial images were used for scoring.

Statistics

All values displayed are mean ± SEM. CT scores before and at diagnosis of CLAD were compared using Wilcoxon's matched pairs test. Evolution of CT throughout time (CT diagnosis of CLAD, at 3 to 12 months after diagnosis and last available CT) were compared using Friedman's test. Survival analysis was performed with Kaplan–Meier curve comparison. Correlation was performed using Spearman's rank test. Spirometric values at the time of high-resolution CT scan were used for the analysis. All statistics was performed using GraphPad Prism, version 4.0 (GraphPad Software, Inc., La Jolla, CA). $p < 0.05$ was considered significant.

Results

Patients' characteristics

Detailed characteristics of patients are presented in Table 1. Twenty-four of the patients were ultimately diagnosed with RAS. At the end of the study period, 5 patients were alive and did not undergo retransplantation, 10 underwent