Computed Tomography in the Evaluation of Lung Transplant Chronic Rejection

Tomografia Computorizada na Avaliação da Rejeição Crónica nos Transplantes Pulmonares

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Abstract
Lung transplantation is an increasingly common therapeutic option in end-stage pulmonary diseases. One of the main causes of medium and long-term graft failure is chronic rejection, clinically represented by bronchiolitis obliterans syndrome. The early diagnosis of chronic rejection allows optimization of immunosuppressive therapy in order to delay its progression.

In this paper, we review and illustrate the characteristics of chronic lung rejection in high-resolution computed tomography to promote its early diagnosis in follow-up examinations.

At an early stage, during the first year after transplantation, subtle features such as reduction of peripheral bronchovascular markers, thickening of the septal lines, and decreased lung volumes may suggest the diagnosis even before clinical changes appear. Mid-term features are represented by bronchiectasis and bronchial wall thickening, and present low sensitivity, but high specificity in the diagnosis of chronic rejection. Its appearance occurs simultaneously with the clinical diagnosis of bronchiolitis obliterans syndrome. Lung attenuation abnormalities appear in late stages of the disease. Air trapping is related with small airway obstruction and mosaic attenuation pattern with ventilation-perfusion mismatch. Fibrotic changes of the lung parenchyma characterize advanced stages of chronic graft rejection, leading to important functional repercussion.

High-resolution computed tomography has helped to overcome the limitations of clinical criteria in the diagnosis of obliterans bronchiolitis syndrome and promoted an earlier diagnosis of chronic rejection after lung transplantation.

Keywords
CT; Lung transplantation; Transplant rejection; Bronchiolitis obliterans.

Resumo
O transplante pulmonar é uma opção terapêutica cada vez mais frequente em doenças pulmonares em estádio terminal. Uma das principais causas de falência do enxerto, a médio e longo prazo, é a rejeição crónica, traduzindo-se sob a forma de síndrome de bronquiolite obliterante. O diagnóstico precoce desta entidade permite otimizar a terapêutica imunossupressora, limitando a sua progressão.

Este trabalho reúne, discute e ilustra as características da rejeição crónica dos enxertos pulmonares na tomografia computorizada de alta resolução, com o objetivo de facilitar o seu reconhecimento em exames de seguimento e, promover o diagnóstico precoce desta entidade.

Numa fase precoce, durante o primeiro ano após o transplante, alterações subclínicas como a redução das marcas broncovasculares periféricas, o espessamento das linhas septais e a diminuição do volume pulmonar podem indicar o diagnóstico, mesmo antes do aparecimento de alterações clínicas. A médio prazo, surgem bronquiectasias e espessamento brônquico, características com baixa sensibilidade, mas de alta especificidade no diagnóstico de rejeição crónica. Seus sinais são detectados simultaneamente ao diagnóstico clínico. No entanto, as alterações de atenuação pulmonar são mais evidentes aos poucos após o diagnóstico clínico. A obstrução das vias aéreas com baixa calibre, associada à desuniformidade de atenuação, são as características distintas desse tipo de rejeição.

A tomografia computorizada de alta resolução tem ajudado a ultrapassar as limitações dos critérios clínicos no diagnóstico da síndrome de bronquiolite obliterante, contribuindo para o diagnóstico precoce da rejeição crónica nos enxertos pulmonares.

Palavras-chave
TC; Transplante pulmonar; Rejeição de transplante; Bronquiolite obliterante.

Introduction
Pulmonary transplantation is currently a therapeutic option that promotes increased survival and quality of life in patients with end-stage pulmonary diseases who meet criteria for this intervention. Complications vary according to temporal progression, the infectious intercurrences being the main cause of mortality
in the first six months after transplantation and chronic graft rejection the main cause of mortality after that period. From the histopathological point of view, chronic rejection is characterized by proliferative submucosal fibrotic changes causing obstruction of the small airways, a process known as bronchiolitis obliterans, which can affect up to 50% of transplanted patients. Chronic rejection has strong associations established with previous episodes of acute rejection and cytomegalovirus infection. Clinically, it may be manifested by progressive worsening cough and dyspnea, associated with decreased FEV1-dependent on the pathology of small airways.

The concept of bronchiolitis obliterans syndrome, defined as the ≥20% reduction in FEV1 in relation to the baseline value after transplantation, was created by the International Society for Heart and Lung Transplantation due to the low sensitivity of lung biopsies in the diagnostic confirmation of chronic rejection of the pulmonary graft. In the differential diagnosis, other causes justifying FEV1 reduction, such as infectious intercurrences or episodes of acute rejection of the graft, should be excluded. This functional evaluation, however, presents some limitations, especially in patients with uni-pulmonary transplants, in which the lung function of the native lung can influence the results obtained.

Early diagnosis of chronic rejection of lung transplantation is essential, since adjustment of immunosuppressive therapy may delay its progression and significantly improve prognosis. Given the limitations associated with clinical and histopathological evaluation, imaging methods, namely computed tomography, have gained prominence in the search for early signs of chronic rejection.

This review paper gathers, discusses and exemplifies the tomographic semiology known to date on chronic rejection in lung transplants, seeking to simplify the approach of the radiologist when confronted with this situation in his clinical practice.

**Imaging findings**

Imaging of pulmonary grafts is performed using serial chest radiographs and computed tomography scans. Radiographic findings of bronchiolitis obliterans, which usually only appear six months after transplantation, are non-specific. They usually consist of segmental atelectasis foci, decrease in peripheral vascular markers and pulmonary volume. However, lung parenchyma and bronchial structures ability to be appreciated is much higher in computed tomography, allowing greater sensitivity in the detection and characterization of chronic alterations.

The onset of bronchiolitis obliterans follows a chronological sequence of changes in computed tomography, which can be organized in early, mid-term and late alterations and are characterized hereafter.

**Early changes**

It is possible to recognize imaging changes suggesting chronic rejection even before the clinical diagnosis of bronchiolitis obliterans syndrome. Among these aspects are the reduction of the peripheral bronchovascular markers (Fig. 1), the thickening of the septal lines (Fig. 2) and the reduction of the volume of the transplanted lung (Fig. 3). These findings usually occur during the first year after transplantation, however, they have limited diagnostic utility in the prediction of chronic rejection due to their subtle and inconstant nature.

**Medium-term changes**

Bronchiectasis (Fig. 4) accompanies the clinical diagnosis of the bronchiolitis obliterans syndrome and is defined as the presence of bronchial dilations with a bronchial-artery ratio greater than 1 or the visualization of the bronchial lumen within 1 cm of the costal pleura. Increased resistance in the small airways caused by obliteration of small bronchial structures is one of the accepted etiologic mechanisms in the formation of bronchiectasis in these
patients. However, frequent acute infectious complications in lung transplant patients are also a known cause of bronchiectasis, which is not related to chronic graft rejection. Thickening of the bronchial wall (Fig. 5) is another aspect frequently observed and often associated with bronchiectasis, and its evaluation is performed subjectively by the radiologist. Both bronchiectasis and thickening of the bronchial wall have low sensitivity but high specificity in the diagnosis of chronic rejection of the pulmonary graft.

Late changes
Changes in normal pulmonary attenuation, such as the presence of air trapping (Fig. 6) or mosaic attenuation pattern (Fig. 7) which typically appear in late phases of chronic rejection, are often associated with advanced stages of the disease and caused by bronchial obliteration and small airway obstruction.

Air trapping
The attenuation of the lung parenchyma depends on the amount of intrapulmonary air, decreasing in inspiration and increasing in the expiration. The presence of air trapping consists in the existence of areas of pulmonary parenchyma in which the increase of attenuation with expiration is smaller than it would be expected. In affected areas, the expected volume reduction between inspiratory and expiratory acquisition is also lower than normal.
In clinical practice, the air trapping evaluation is usually qualitative. Several studies have been developed to eliminate the subjectivity of this type of evaluation and to find useful semiquantitative and quantitative measures. Among these studies, Bankier et al determined the threshold of 33% of the parenchyma affected by air trapping as the value from which computed tomography allows the diagnosis of bronchiolitis obliterans syndrome to be predicted in a sensitive, specific and accurate manner, even before clinical appearance. Knollmann et al showed that it is possible to use quantitative measures to predict the diagnosis of bronchiolitis obliterans syndrome using a spirometric gating method, but the complexity of this technique has limited its application to current clinical practice.

Notes and technical aspects useful in evaluating air trapping:
1) The attenuation of the pulmonary parenchyma decreases from the bases to the apex of the lungs and is more homogeneous in inspiration.
2) During exhalation, it is possible to observe some areas of air trapping in healthy individuals, especially in locations adjacent to the small cissure or in the apical segments of the lower lobes.
3) In an individual assessment over time, air trapping is an inconstant finding in a significant number of patients.
4) For proper detection of air trapping it is essential to compare acquisitions in inspiration and expiration.
5) It is not recommended to limit expiratory acquisition to some images in predefined sections as it is usual in the study of other pulmonary pathologies. The heterogeneous distribution of the changes related to the bronchiolitis obliterans syndrome necessitates the study of the full extent of the pulmonary parenchyma, even at expiration.
6) Prior patient training of breath-hold at maximal inspiratory and expiratory positions contributes to acquisition at appropriate ventilatory times and reduces movement artifacts.

Mosaic attenuation pattern
The mosaic attenuation is defined by the presence of areas of low attenuation of the pulmonary parenchyma intercalated by areas of normal attenuation, in the acquisition in inspiration. The areas of lower attenuation result from decreased vascularization due to ventilation-perfusion changes.

The mosaic attenuation pattern has low sensitivity but high specificity in the diagnosis of bronchiolitis obliterans syndrome, similar to that observed in the presence of bronchiectasis or thickening of the bronchial wall.

Graft fibrosis
With the progression of the bronchiolitis obliterans syndrome to the terminal stages of the disease, aspects such as thickening of the septal lines, loss of lung volume or bronchiectasis culminate in irreversible fibrotic changes (Fig. 8).

When the fibrotic alterations are focused on the upper lobes, they constitute a distinct rare entity associated with chronic pulmonary rejection, which arises 1 to 4 years after transplantation and is characterized by thickening of the interlobular septa, reticular and ground glass opacities, traction bronchiectasis, honeycombing, architectural distortion and loss of lung volume.

Figure 8 - End-stage chronic lung rejection in a 47-year-old woman with bronchiolitis obliterans syndrome, two years after bilateral lung transplantation. In the image, coarse reticulation is evident, associated with architectural distortion, traction bronchiectasis and significant loss of lung volume

Conclusion
The radiologist plays a leading role in the evaluation of patients undergoing lung transplantation and should be familiar with the temporal progression of the main imaging findings related to chronic rejection.

In the evaluation of the transplanted pulmonary patient, parenchymal alterations related to the reduction of the peripheral bronchovascular markers, thickening of the septal lines, loss of volume, bronchiectasis, bronchial wall thickening, air trapping or mosaic attenuation pattern should make the hypothesis of bronchiolitis obliterans syndrome be considered. Fibrotic changes of the pulmonary parenchyma are of relevance in the advanced stages of chronic rejection.

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