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Review Article / Artigo Revisão

Computed Tomography in the Evaluation of Lung Transplant Chronic Rejection

Tomografia Computorizada na Avaliação da Rejeição Crónica nos Transplantes Pulmonares

João Lopes, Marta Simões

Serviço de Radiologia, Hospital de Santa Marta, Centro Hospitalar Lisboa Central, Lisboa, Portugal

Address

João Lopes
Serviço de Radiologia
Hospital de Santa Marta, Centro Hospitalar Lisboa Central
Rua de Santa Marta 50
1169-024, Lisboa, Portugal
e-mail: jpa.lopes@gmail.com

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 subtis como a redução das marcas broncovasculares periféricas, o espessamento das linhas septais e a diminuição do volume pulmonar podem indiciar o seu diagnóstico, mesmo antes do aparecimento de alterações clínicas. A médio prazo, aquando do diagnóstico clínico, podem observar-se bronquiectasias e espessamento brônquico, características com baixa sensibilidade, mas de alta especificidade no diagnóstico da rejeição crónica. As alterações da atenuação pulmonar surgem em fases mais avançadas desta síndrome, evidenciando padrão de retenção aérea por obstrução das pequenas vias respiratórias, associado a padrão de atenuação em mosaico, condicionado por alterações da ventilação-perfusão. Tardiamente, a rejeição crónica do enxerto caracteriza-se por alterações fibróticas do parênquima pulmonar com importante repercussão funcional.
A tomografia computorizada de alta resolução tem ajudado a ultrapassar as limitações dos critérios clínicos no diagnóstico da síndrome de bronquiolite obliterante e promovido o diagnóstico mais precoce da rejeição crónica dos 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.[1]
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.[2]
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.[3]
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.[4]
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.[5] 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.[3]
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.[6,7]
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.[4] 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.[3,8]
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.[3]

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.[3]

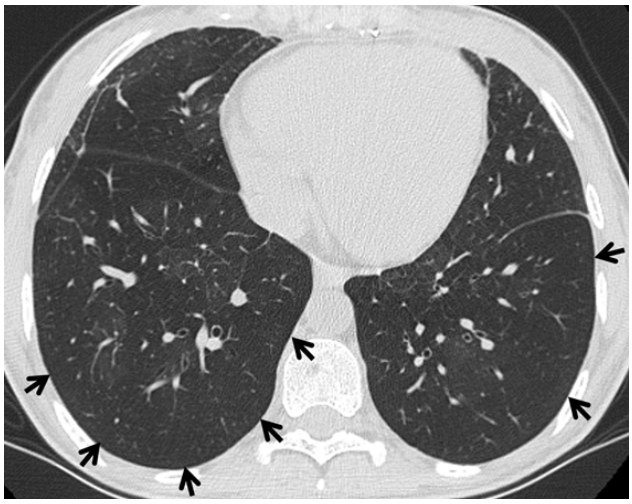

Figure 1 - A 27-year-old woman with bronchiolitis obliterans syndrome after bi-pulmonary transplantation. In this high-resolution axial image obtained one year after transplantation, the bronchovascular markers are reduced to the periphery, affecting mainly the posterior areas of the lower lobes. Additionally there is discrete pattern of mosaic attenuation.

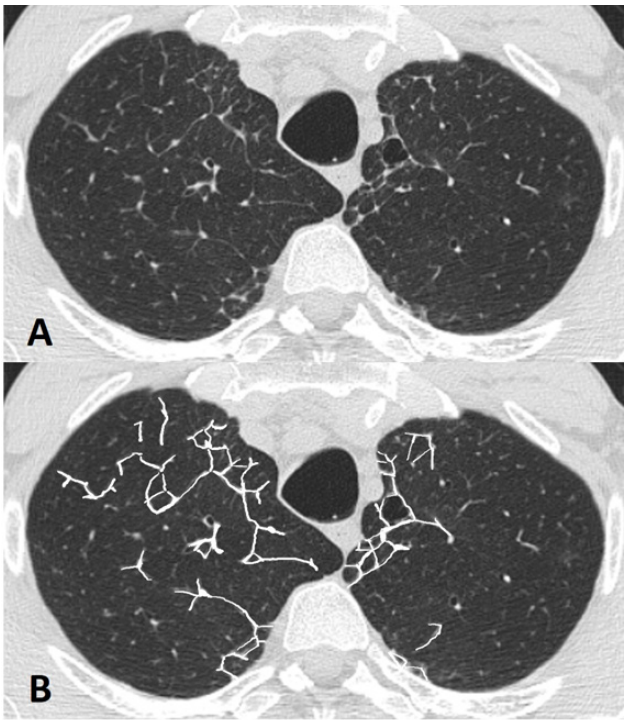

Figure 2 - Thickening of septal lines in a 37-year-old man with bronchiolitis obliterans syndrome after bi-pulmonary transplantation. High resolution axial image (A) obtained 5 and a half years after transplantation, where the acinar anatomy is evidenced due to the thickening of the intralobular and interlobular septa. These changes are illustrated in B.

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.[9]
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

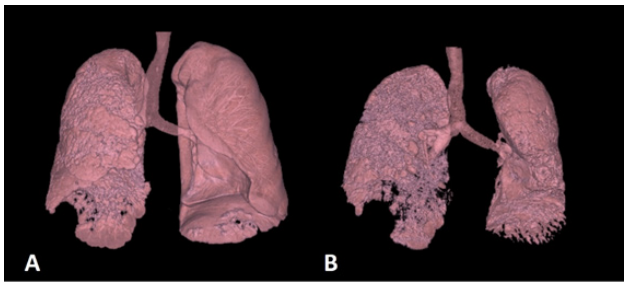

Figure 3 - Three-dimensional reconstructions (volume rendering technique) in men submitted to left uni-pulmonary transplantation, 4 months (A) and 4 years (B) after transplantation. Between the two evaluations there is marked volumetric reduction of the graft resulting from chronic rejection. There is also a volumetric reduction of the native right lung, although to a lesser degree, probably related with the descamative interstitial pneumonia which led transplantation.

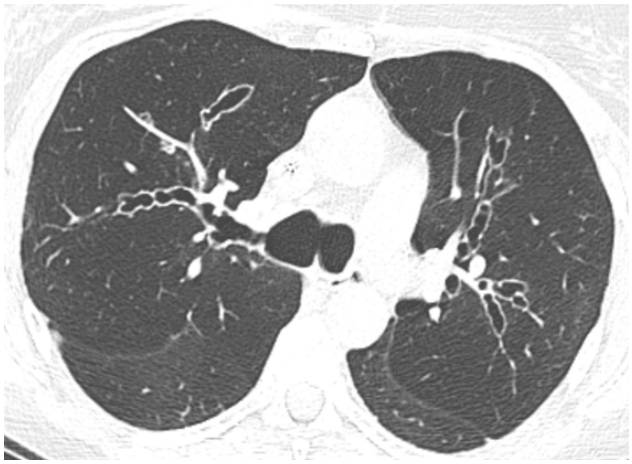

Figure 4 - Bilateral varicose bronchiectasis in a woman with bronchiolitis obliterans syndrome, after bilateral lung transplantation, one and a half years before the examination. Note the associated bronchial thickening.

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.[3] 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.[9] Both bronchiectasis and thickening of the bronchial wall have low sensitivity but high specificity in the diagnosis of chronic rejection of the pulmonary graft.[7,9]

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.[3]

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.[10,11]

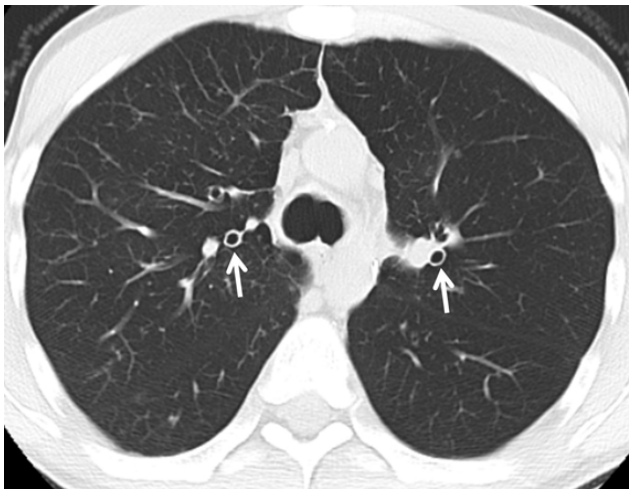

Figure 5 - Bronchial wall thickening (arrows) in a man with bronchiolitis obliterans syndrome, submitted six years before to bilateral lung transplantation.

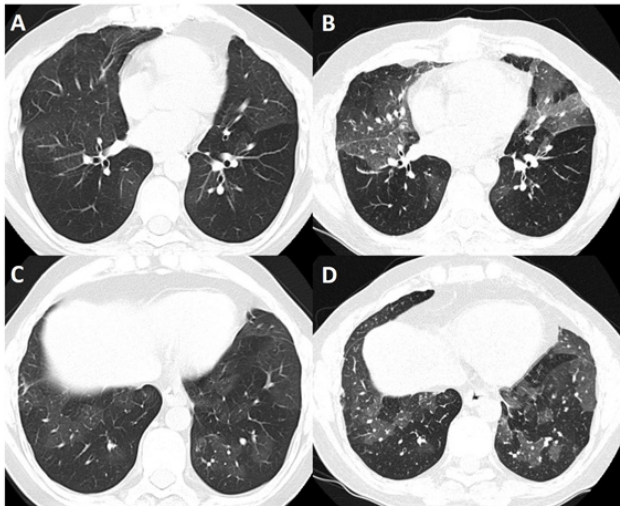

Figure 6 - Examples of air trapping in two different segments, in a man with bronchiolitis obliterans syndrome three years after bi-pulmonary transplantation. Changes in pulmonary parenchymal attenuation are mild on inspiration acquisition (A, C). At the end of the expiration air trapping becomes evidently marked (B, D). The areas with the highest density correspond to areas of normal attenuation.

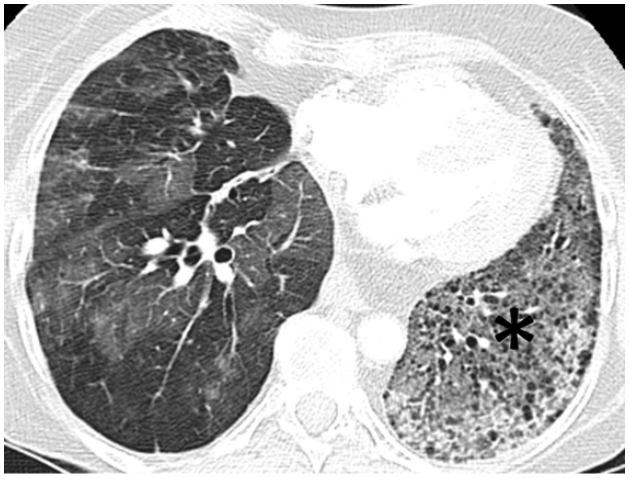

Figure 7 - Acquisition in inspiration showing mosaic attenuation pattern in a woman with bronchiolitis obliterans syndrome four years after right unilateral lung transplantation. Native left lung with advanced stage changes due to extrinsic allergic alveolitis (*).

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.[10]
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.[9,11]
3) In an individual assessment over time, air trapping is an inconstant finding in a significant number of patients.[9]
4) For proper detection of air trapping it is essential to compare acquisitions in inspiration and expiration.[6]
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.[10]

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.[9]

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.[1,2]

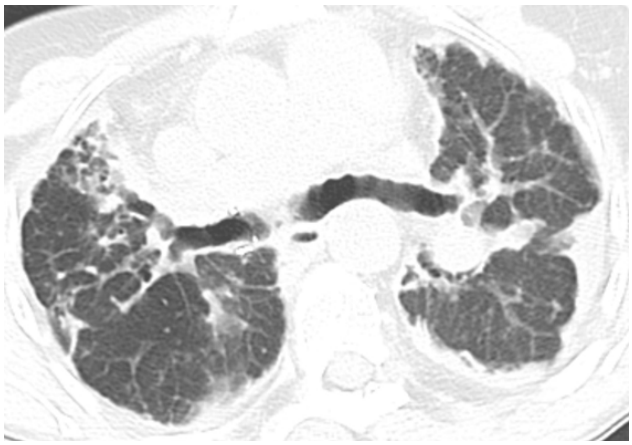

Figure 8 - End-stage chronic lung rejection in a 47-year-old woman with bronchiolitis obliterans syndrome, two years after bilateral lung transplantation. In the image, coarse reticulation is evident, associated with architectural distortion, traction bronchiectasis and significant loss of lung volume

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 patternshould 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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Confidencialidade dos dados: Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação dos dados de doentes.
Protection of human and animal subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).
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References

1. Ng YL, Paul N, Patsios D, Walsham A, Chung T-B, Keshavjee S, et al. Imaging of lung transplantation: review. AJR Am J Roentgenol. 2009;192: S1-13.
2. Krishnam MS, Suh RD, Tomasian A, Goldin JG, Lai C, Brown K, et al. Postoperative complications of lung transplantation: radiologic findings along a time continuum. Radiographics. 2007;27:957–74.
3. Ikonen T, Kivisaari L, Taskinen E, Piilonen A, Harjula AL. High-resolution CT in long-term follow-up after lung transplantation. Chest. 1997;111:370–6.
4. Murray JG, McAdams HP, Erasmus JJ, Patz EF, Tapson V. Complications of lung transplantation: Radiologic findings. Am J Roentgenol. 1996;166:1405–11.
5. Cooper JD, Billingham M, Egan T, Hertz MI, Higenbottam T, Lynch J, et al. A working formulation for the standardization of nomenclature and for clinical staging of chronic dysfunction in lung allografts. International Society for Heart and Lung Transplantation. J Hear Lung Transpl. 1993;12:713–6.
6. Siegel MJ, Bhalla S, Gutierrez FR, Hildebolt C, Sweet S. Post-lung transplantation bronchiolitis obliterans syndrome: usefulness of expiratory thin-section CT for diagnosis. Radiology. 2001;220:455–62.
7. Leung AN, Fisher K, Valentine V, Girgis RE, Berry GJ, Robbins RC, et al. Bronchiolitis obliterans after lung transplantation: Detection using expiratory HRCT. Chest. 1998;113:365–670.
8. Worthy SA, Park CS, Kim JS, Muller NL. Bronchiolitis obliterans after lung transplantation: high-resolution CT findings in 15 patients. AJR Am J Roentgenol. 1997;169:673–7.
9. Konen E, Gutierrez C, Chaparro C, Murray CP, Chung T, Crossin J, et al. Bronchiolitis obliterans syndrome in lung transplant recipients: can thin-section CT findings predict disease before its clinical appearance? Radiology. 2004;231:467–73.
10. Knollmann FD, Ewert R, Wündrich T, Hetzer R, Felix R. Bronchiolitis obliterans syndrome in lung transplant recipients: use of spirometrically gated CT. Radiology. 2002;225:655–62.
11. Bankier AA, Van Muylem A, Knoop C, Estenne M, Gevenois PA. Bronchiolitis obliterans syndrome in heart-lung transplant recipients: diagnosis with expiratory CT. Radiology. 2001;218:533–9.