Case report

Trajectory of lung function to pleuroparenchymal fibroelastosis late after haematopoietic stem-cell transplantation

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1. Introduction

Pleuroparenchymal fibroelastosis (PPFE) is a rare life-threatening disease affecting the visceral pleura and sub-pleural parenchyma of upper lung regions [1]. Early diagnosis of this disease is important because it carries a poor prognosis and may require lung transplantation in severe cases. The histopathological and radiological features of PPFE have been well described [2] and its characteristic lung function pattern is a restrictive abnormality, i.e., decreased total lung capacity (TLC), associated with decrement of lung diffusing capacity for carbon monoxide (DLCO) [2]. PPFE has been reported as idiopathic [3] or as a complication of various conditions including haematopoietic stem-cell transplantation (HSCT) [4], but its pathophysiology is still elusive [5].

We hereby report the pulmonary function tests (PFTs) trajectory in a patient receiving allogenic HSCT, who first developed idiopathic pneumonia syndrome (IPS), then bronchiolitis obliterans syndrome (BOS) and finally late PPFE. In order to make lung function changes comparable, respiratory parameters were expressed as z-scores which indicate how many standard deviations a given measure differs from its predicted value.

2. Case report

In 2005, a 30-year-old, never-smoker, Caucasian woman with normal body mass index (BMI: 20 kg·m⁻²) was diagnosed with Hodgkin's lymphoma. She received chemotherapy and autologous HSCT and, one year later, allogeneic HSCT preceded by a myeloablative treatment including cyclophosphamide, cyclosporine A, methotrexate and 12 Gy total body irradiation (TBI). PFTs were all within their respective normality range before allogenic HSCT (Fig. 1), but at 3-month follow-up they revealed a moderate decrement of TLC (3.70 L; 72% of predicted; z-score: -2.47), forced vital capacity (FVC) (2.63 L; 66% of predicted; z-score: -2.95), forced expiratory volume in 1 second (FEV1) (1.53 L; 64% of predicted; z-score: -3.00), and DLCO (8.95 mmol·L⁻¹·min⁻¹·kPa⁻¹; 66% of predicted; z-score: -2.16). The longitudinal changes of lung function preceding this complication have not been described. We report the case of an adult woman undergoing allogeneic HSCT for Hodgkin's lymphoma. Pulmonary function tests evolved from normal, before transplantation, to a restrictive pattern with normal residual volume 3 months after transplantation, then to an obstructive pattern consistent with bronchiolitis obliterans 18 months after transplantation, and finally to a severe mixed pattern with preserved residual volume. Computed tomography showed the distinctive features of pleuroparenchymal fibroelastosis, confirmed by histology of specimen from apical resection after pneumothorax. This case report suggests that pleuroparenchymal fibroelastosis may occur after HSCT following bronchiolitis obliterans syndrome with a mixed (restrictive-obstructive) lung function pattern.
predicted; z-score: -2.80), forced expiratory volume in 1 s (FEV₁) (2.21 L; 67% of predicted; z-score: -2.72) and DLCO (15.6 mL·min⁻¹·mmHg⁻¹; 67% of predicted; z-score: -2.70) whereas residual volume (RV) was within the normal range but increased from pre-HSCT value, thus resulting in an RV % of predicted to TLC % of predicted ratio (RV/TLC) of 140%. This pattern and computed tomography (CT) scan findings were considered consistent with IPS and eventually treated with oral corticosteroids in addition to maintenance cyclosporine A.

Fig. 1. A) Representative maximal expiratory flow versus absolute lung volume (MEFV) curves before and at various time intervals after allogeneic haematopoietic stem-cell transplantation (HSCT). It is noteworthy the rightward shift of MEFV curves following HSCT. B) Trajectory of lung function after HSCT. The shaded area represents normality range with upper and lower bounds corresponding to the higher (1.645 z-score) and lower (−1.645 z-score) limits of normal, i.e., the 5th and 95th percentiles, respectively, of the relevant reference values. IPS: idiopathic pneumonia syndrome; BOS: bronchiolitis obliterans syndrome; PPFE: pleuroparenchymal fibroelastosis; RV: residual volume; FEV₁/FVC: forced expiratory volume in 1 s-to-forced vital capacity ratio; TLC: total lung capacity; DLCO: single-breath lung diffusing capacity for carbon monoxide.

Fig. 2. A) Computed tomography (CT) scan at tracheal carina showing features of pleuroparenchymal fibroelastosis. B) Automatic quantitative 3D analysis of the entire lungs. It is noteworthy, the significant extent of high attenuation areas (HAA >200 HU) consistent with fibrosis (16% of CT volume) and the lack of low attenuation areas (LAA < -950 HU) consistent with emphysema. C) Low-power (20 x), haematoxylin and eosin staining, micrograph showing visceral pleural fibrosis and elastosis, with sharp demarcation from normal lung parenchyma (black arrow). Neither granulomas nor inflammation appears in areas of fibrosis. D) High-power (100 x), elastic Van Gieson staining, micrograph showing an artery (black arrow) with a double layer of elastic fibers in the wall, thickening of media, and sub-occlusion of the lumen.
Over the following months, the patient experienced progressive exertional dyspnea with dry cough. At 18-months follow-up, PFTs showed the new onset of a severe (FEV₁: 1.80 L; 48% of predicted; z-score: -4.01) obstructive abnormality with borderline decrement of FEV₁/FVC ratio (0.72; z-score: -1.73) and TLC (4.03 L; 78% of predicted; z-score: -1.91) but RV still within the normal range. Thereafter, TLC returned above the lower limit of normal but FEV₁/FVC further decreased, without significant bronchodilator response to 400 μg inhaled salbutamol, while RV/TLC remained > 120%. These findings, in the absence of respiratory infections, supported a diagnosis of BOS. A course of inhaled fluticasone/formoterol, oral azithromycin, montelukast, and corticosteroids led to symptom relief. At 7-year follow-up, chest auscultation revealed short wheezes preceded by crackles from mid-to-end inspiration over the lower lung zones bilaterally and full-expiration CT showed bilateral mosaic hypo-attenuation areas suggestive of air trapping. Subsequently, over the next five years TLC and DLCO decreased progressively, while severe obstruction persisted and RV tended to decrease. At 12-year follow-up, TLC and DLCO were severely decreased while RV/TLC was 149% and FEV₁/FVC marginally reduced. CT scans showed “wedge-shaped” pleural thickening of upper and middle lung zones bilaterally, with reticular fibrotic pattern involving 16% of lung volume, without inspiratory low-attenuation areas suggestive of emphysema (Fig. 2A and B). Three months later, the patient had a right pneumothorax requiring apical resection by video-assisted thoracoscopic surgery. Histology showed fibro-elastosis of sub-pleural lung parenchyma and visceral pleura, with no inflammation, or granulomas, or emphysematous areas (Fig. 2C and D). Eventually, her condition improved and she was discharged from the hospital.

3. Discussion

Patients undergoing HSCT preceded by myeloablative chemotherapy and TBI are susceptible to develop severe non-infectious pulmonary complications including BOS [6], IPS [7] and, more rarely, PPFE [4,5]. The clinical manifestations of these complications (exertional dyspnea, cough and wheezing) are often related to chronic graft-versus-host disease (GvHD) but not specific or even absent in the early phases. For this reason, the 2014 National Institutes of Health consensus recommended frequent PFTs starting from day 100 after HSCT [8].

PPFE has been previously described as a restrictive disorder, differing from interstitial pulmonary fibrosis for an increased RV/TLC ratio [9], thus with an FVC decrement disproportionate to the reduction of TLC. This pattern has been recently defined as “complex” restriction [10] resulting from incomplete lung emptying due to neuromuscular disease, chest wall limitation, or occult air trapping. In the present case, a restrictive pattern with increased RV/TLC was present as early as 3-months after transplantation, when IPS was diagnosed. Thereafter, RV/TLC remained persistently increased either in association with obstructive (reduced FEV₁/FVC, normal TLC) or mixed (both FEV₁/FVC and TLC decreased), up to the time when the diagnosis of PPFE was made. As the patient had normal BMI, no chest wall abnormalities, and normal tests of respiratory muscle strength (maximal inspiratory mouth pressure: -67 cmH₂O; maximal expiratory mouth pressure: 77 cmH₂O), the persistent increase of RV/TLC, either associated with normal or reduced FEV₁/FVC was likely the result of air trapping due to obstructive bronchiolitis. Alkylation and radiation treatments have also been hypothesized as possible causes of PPFE after HSCT [11] but this was unlikely in our case because no such treatments were given after allogeneic HSCT and PPFE was preceded by BOS.

In conclusion, the lung function trajectory of this case suggests that PPFE occurred late after HSCT because of persistent oblitative bronchiolitis, thus resulting in a mixed (restrictive-obstructive) abnormality.

Conflicts of interest

All authors declare no conflict of interest.

Informed consent

Informed consent was obtained from the participant included in the study including for use of images in publication.

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