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Ertapenem may be useful for MDR/XDR-TB to simplify administration of carbapenem when the patient is at home <http://ow.ly/Snx69>

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Restrictive chronic lung function decline after haematopoietic stem cell transplantation



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To the Editor:

Until recently, it was generally thought that bronchiolitis obliterans syndrome (BOS), which is a type of obstructive lung disease with a dismal outcome, was the sole form of chronic lung allograft dysfunction

(CLAD) occurring after lung transplantation. However, recent publications reported that some patients experience a restrictive form of chronic lung complication that has been termed restrictive allograft syndrome (RAS) [1]. Approximately one-third of patients with CLAD after lung transplantation can be classified as having RAS [2, 3]. This distinct form of CLAD is considered to be an important entity and has features that are distinct from those of BOS. First and foremost, the mortality of RAS is even greater than that from BOS: a previous study reported that the survival of patients with RAS was significantly poorer than that of patients with BOS [3]. Secondly, imaging of BOS on computed tomography (CT) has revealed air trapping, tree-in-bud opacities and peribronchial infiltrates, whereas RAS presented mainly with alveolar or interstitial changes such as septal thickening or reticulation [4]. Additionally, RAS has been histologically characterised by diffuse alveolar damage and extensive fibrosis in the alveolar interstitium and interlobular septa [2].

Lung transplantation is not the only cause of BOS; that is, BOS can also develop after haematopoietic stem cell transplantation (HSCT) [5]. We speculated therefore that a restrictive form of chronic lung complication might also occur after HSCT and aimed to investigate whether a chronic, restrictive lung complication can indeed develop in HSCT recipients and, if so, to identify its characteristics.

We recruited study subjects who underwent HSCT at Asan Medical Center, a 2700-bed referral hospital in Seoul, South Korea, between December 1993 and November 2013. In total, 1352 patients were initially recruited into our study, leading to a final number of participants of 1187 (figure 1). The medical records of these patients were analysed retrospectively in June 2014. Our current study protocol was approved by the Institutional Review Board of Asan Medical Center.

Chronic lung function decline (CLFD) is defined as a reduction of >20% compared with the corresponding baseline values at the time of HSCT of the average of the two best pre-bronchodilator forced expiratory volumes in 1 s (FEV₁) and/or forced vital capacity (FVC) measurements taken ≥3 weeks apart. In all patients, BOS and restrictive CLFD (R-CLFD) were diagnosed on the basis of pulmonary function test results. The criteria for defining BOS were 1) the presence of CLFD, 2) a FEV₁/FVC ratio <0.7, and 3) the absence of an identifiable cause of lung function decline, such as infection. The criteria for R-CLFD were 1) the presence of CLFD, 2) a FEV₁/FVC ratio ≥0.7 and 3) the absence of an identifiable cause.

The mean age of the 1187 patients with HSCT was 39.0 years and men predominated (56.3%, 668 out of 1187 patients). Acute leukaemia was the most common indication for HSCT (64.3%, 763 out of 1187 patients).

After excluding identifiable causes, 88 patients were diagnosed with CLFD during a median follow-up period of 42.5 months (interquartile range (IQR) 19.7–60.0 months) after HSCT (figure 1). Of these, BOS developed in 82 (93.2%) patients at a median of 12.3 months (IQR 8.8–21.1 months) after HSCT. At a median of 30.3 months (IQR 15.2–51.5 months) after HSCT, another six (6.8%) patients were diagnosed

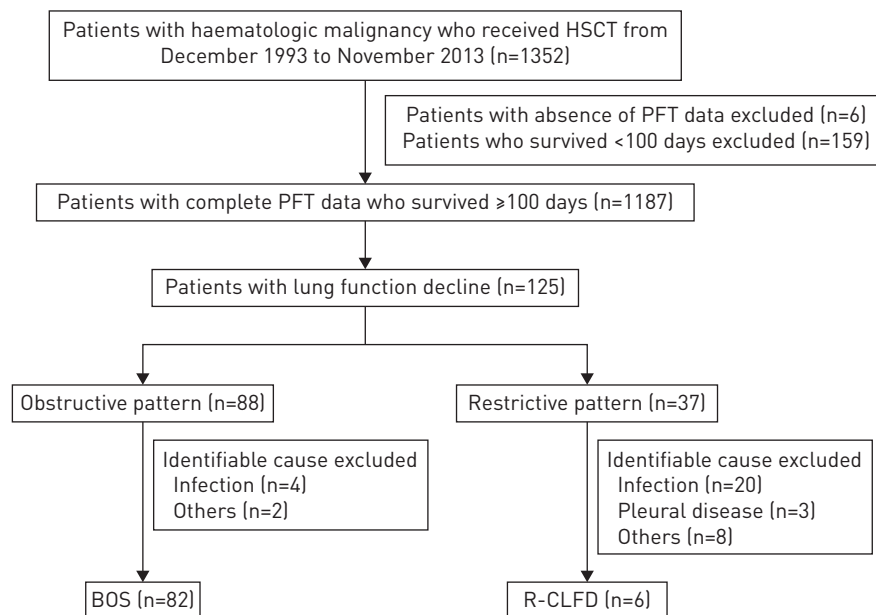


FIGURE 1 Screening and enrolment of study patients. HSCT: haematopoietic stem cell transplantation; PFT: pulmonary function test; BOS: bronchiolitis obliterans syndrome; R-CLFD: restrictive chronic lung function decline.

with R-CLFD. Baseline characteristics were comparable between the six patients with R-CLFD and the 82 BOS cases. All patients with BOS had evidence of chronic graft-versus-host disease (GVHD) at another site, such as the skin or liver.

Excluding the three patients who received a lung transplant, the survival of the remaining 79 patients with BOS was compared with that of the six patients with R-CLFD. A total of 26 (32.9%) BOS patients died, mostly from infection, and the median survival of the 79 patients with BOS was 20.0 months (IQR 5.7–40.3 months) from diagnosis. In contrast, the median survival time of the six R-CLFD patients was 42.3 months (IQR 29.1–100.2 months) from diagnosis ($p < 0.001$ compared with BOS) and one (16.7%) patient died of septic shock due to pneumonia.

For those BOS patients who were investigated by chest CT, the findings were consistent with their diagnosis: namely, mosaic attenuation, hyperlucent lung parenchyma, bronchial wall thickening and centrilobular lung nodules. In contrast, radiological examination of R-CLFD showed slowly progressive fibrotic changes mainly involving alveolar units. These changes usually started with ground-glass opacities or consolidation of the peripheral lung and were followed by gradually increased interstitial reticulation, before finally progressing to volume loss and architectural distortion with traction bronchiectasis.

To the best of our knowledge, our current study is the first to report chronic lung complications of a restrictive type in patients who have received HSCT. The most important finding of our present analyses was that some patients presented with a restrictive form of CLFD after HSCT.

Our CT findings were consistent with those previously reported for RAS after lung transplantation [6], and our patients with RAS and R-CLFD showed the same restrictive pulmonary physiology. However, we found that some features of R-CLFD and BOS after HSCT differed from those of RAS and BOS after lung transplantation. Above all, the incidence of R-CLFD was only 6.8% in the 88 patients in our CLFD group that combined BOS and R-CLFD. Besides this, the survival of patients with R-CLFD was significantly better than that of patients with BOS. These features contrast with those of R-CLAD after lung transplantation.

BOS is associated with constrictive bronchiolitis that targets conducting airways while sparing terminal bronchioles and the alveolar surface [7], whereas the lung changes mainly developed in alveolar units in R-CLFD in our present study. This disparity in anatomical involvement sites suggests that the pathobiological mechanisms of R-CLFD after HSCT are different from those of BOS, which is considered to be a manifestation of chronic GVHD. Todd *et al.* [3] have reported that patients with R-CLAD after lung transplantation were more likely to have newly detected human leukocyte antigen (HLA) antibodies than those with BOS, which may have humoral responses that directly target alveolar antigens. In this context, we believe that the reason for the different incidence of restrictive chronic lung complications between post-HSCT and post-lung transplantation patients might be partly explained by the presence of anti-HLA antibodies; that is, in contrast to lung transplantation, where HLA matching is not usually a concern, HLA matching is strongly recommended in HSCT. Indeed, in the 1187 patients who were included in our current analysis, 769 (64.8%) patients and 350 (29.5%) patients received matched sibling and matched unrelated HSCT, respectively.

We excluded patients with infection as the identifiable cause before a CLFD diagnosis. In these patients, the infection had been appropriately treated and lung function subsequently recovered in most cases. None of the six patients with R-CLFD experienced symptoms suggestive of infection when early radiological changes such as ground-glass opacities or consolidation occurred.

In conclusion, we here report that a restrictive type of lung function decline can develop as a chronic lung complication of HSCT in a subset of patients. This distinct type of CLFD seems to have features that differ from those of BOS after HSCT in terms of radiological findings, incidence and survival.



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Some patients present with restrictive chronic lung function decline after haematopoietic stem cell transplantation <http://ow.ly/RpsAx>

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Detection of pepsin in sputum: a rapid and objective measure of airways reflux

To the Editor:

The diagnostic test, Peptest (RD Biomed Ltd, Cottingham, UK), detects pepsin in expectorated saliva and is established as a simple, noninvasive measure of reflux of gastric contents. It has been used to detect pepsin A in patients with both gastro-oesophageal reflux disease (GORD) and extra-oesophageal reflux into the laryngopharynx and airways [1–5].

Reflux has a substantial, but as yet undefined, component in the aetiology of cough hypersensitivity syndrome [6]. Currently evaluation is by the subjective Hull Airways Reflux Questionnaire (HARQ) [7] or objective, but costly and invasive, measures such as 24-h pH-metry, impedance [8], and high resolution manometry [8, 9]. These current diagnostic pathways have their limitations in detecting low levels of airways reflux that may be sufficient to cause chronic cough. We hypothesised that Peptest could provide simple objective confirmation of airways reflux in unselected patients with chronic cough.

Peptest was used in routine clinical practice in out-patients attending the Hull Cough Clinic at Castle Hill Hospital (Hull, UK), a secondary and tertiary referral centre. Verbal consent was obtained at the time of attendance. Chronic cough was defined as cough lasting >8 weeks.

Patients were instructed to provide three expectorated saliva/sputum samples into sample collection tubes (containing 0.01M citric acid) during daily activities and immediately after three spontaneous coughing episodes. Sample collection was optimised by providing patient leaflets and a video. The presence and concentration of pepsin was measured using Peptest by trained analysts and with a lateral flow-test reader calibrated with known concentrations of pepsin A standard. The lower limit of detection is 16 ng·mL⁻¹ and upper limit of quantification was 500 ng·mL⁻¹. Peptest is specific for pepsin A (isoforms 1, 3a, 3b and 3c) and does not detect pepsin C/Gastricsin (isoform 5) putatively suggested to be expressed in the lungs [10, 11]. As pepsin concentrations do not follow a normal distribution a non-parametric statistical analysis was performed.

We have tested 93 (55 female) chronic cough patients mean±SD age 58.4±13.8 years between August 2014 and December 2014. Smoking status was: smoker n=5, nonsmoker n=55, ex-smoker n=24 and unknown n=9. The mean±SD HARQ score (upper limit of normal 13) was 31.9±13.1 and cough duration was 5.6±7.0 years. Over a period of 4 months the 93 patients provided 262 evaluable samples for testing. 80 patients had at least one pepsin positive sample (86.0%). Pepsin concentrations ranged from 0 to 500 ng·mL⁻¹ with a median (interquartile range (IQR)) of 31 ng·mL⁻¹ (0–113.5) ng·mL⁻¹.

We previously [1] used a similar triple sampling strategy in a thoroughly investigated normal asymptomatic healthy volunteer population. The absence of gastro-oesophageal reflux was confirmed by pH-impedance testing. In contrast to this chronic cough study these control samples were provided first thing in the morning, 1 h after lunch and 1 h after the evening meal. Of the 87 control subjects only 33 were found to have at least one positive sample (37.9%) but the pepsin concentration in those that were Peptest positive was very low, median (IQR) of 0 (0–0) ng·mL⁻¹ pepsin, which represents physiological reflux.