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Dichotomy in pulmonary graft-*versus*-host disease evident among allogeneic stem-cell transplant recipients undergoing lung transplantation

To the Editor:

Allogeneic haematopoietic stem-cell transplantation (HSCT) has become a life-saving treatment option for numerous benign and malignant diseases, with more than 14 500 procedures being performed annually in Europe alone [1]. Late-onset noninfectious pulmonary complications (NIPCs) have emerged as the main hurdle to long-term survival, affecting up to 26% of HSCT recipients and conferring 2- and 5-year survival rates of 44% and 13%, respectively [2, 3].

Current diagnostic criteria remain based on those proposed by the National Institutes of Health (NIH) in 2005 for pulmonary graft-*versus*-host disease (GvHD), which considered bronchiolitis obliterans exclusively accountable [4, 5]. Whilst histological confirmation was encouraged, invasive diagnostics have remained contentious due to reported complication rates from open lung biopsies and limited interpretability of trans-bronchial biopsies [6, 7].

Inevitably, surrogate parameters such as new-onset airway obstruction on spirometry and "air-trapping" on computed tomography (CT) have gained precedence in establishing a diagnosis. NIH guidance for monitoring pulmonary GvHD currently incorporates the lung function score that assesses symptoms, forced expiratory volume in 1 s (FEV_1) and diffusing capacity of the lung for carbon monoxide. Currently, diagnosis of pulmonary GvHD requires [4]: 1) FEV_1/forced vital capacity (FVC) <0.7, FEV_1 <75% predicted or residual volume >120% predicted; 2) high-resolution CT demonstrating air trapping, small airway thickening or bronchiectasis; 3) exclusion of infection; and 4) chronic GvHD in at least one extrapulmonary site.

Recently, evidence has emerged suggesting the presence of an additional restrictive form, due to interstitial disease rather than skin GvHD of the chest wall, as has been previously suggested [8, 9]. Through novel assessment of explanted native lungs from patients undergoing lung transplantation (LTx) for end-stage lung disease following allogeneic stem cell transplantation, we compared clinical, radiographic and histological data in this sub-group in an attempt to improve understanding of the pathological processes involved.

Patients who underwent cadaveric LTx between May 1, 2003 and May 1, 2014 at 12 European centres were included. Clinical, imaging and pathological data were collected using standardised reporting forms to facilitate central retrospective analysis. Spirometry was performed in accordance with American Thoracic

Society/European Respiratory Society guidelines, with final values prior to LTx being used in the analysis [10]. CT scans were reported locally for evidence of air trapping, emphysema, ground-glass opacities, bronchiectasis, interstitial changes or lymphadenopathy using accepted criteria [11]. Local pathologists assessed explanted lungs for airway epithelial injury, granulation tissue formation, cicatrix formation, perivascular or alveolar septal inflammation, airspace exudates or hyaline membrane formation [12]. Where possible, retained specimens were re-assessed for pleuroparenchymal fibroelastosis (PPFE) [13, 14]. Based on histological features, patients were designated as exhibiting either airway-limited bronchiolitis obliterans or combined airway and interstitial disease, with the latter being termed fibrotic NIPC.

Categorical variables were analysed using Chi-squared or Fisher's exact test. Continuous variables are expressed as median (interquartile range) and were analysed using either the Mann–Whitney or Wilcoxon tests. Reported p-values are two-tailed, with <0.05 being considered statistically significant.

In total, 60 patients (35 (58%) male) with a median age at LTx of 25.8 (13.6–35.8) years were included (table 1). Nine (15%) patients were aged <18 years at LTx and six (10%) had undergone HSCT due to non-malignant disease. The median interval between HSCT and LTx was 74.5 (37.3–134.1) months. Explanted lungs from all patients were available, with 55 (92%) demonstrating bronchiolitis obliterans. However, in 29 (53%) of these patients extensive interstitial fibrosis was evident and a further five patients demonstrated fibrosis in the absence of bronchiolitis obliterans.

Considering these 34 patients collectively as representing the FIB phenotype, near identical final pre-LTx FEV_1 % pred values were observed in both groups (p=0.824). Similarly, both demonstrated a decline in FVC, although this was more pronounced in FIB (38% *versus* 46%; p=0.014). Total lung capacity (TLC) values were available for 31 patients and proved most discriminatory, with TLC loss characterising FIB patients and hyperinflation bronchiolitis obliterans (74% *versus* 118%; p=0.004). Taking ⩽90% pred as the cut-off, TLC had the best positive predictive value at 0.91, with a negative predictive value of 0.60, which was comparable to that obtained using an FEV_1/FVC >0.7. Skin GvHD was evident in 27 (45%) out of 60 patients but did not correlate with restrictive ventilatory defects (p=0.816).

Air trapping on CT was evident in 34 (57%) out of 60 patients with no difference in prevalence between groups (p=0.305). Other than interstitial change, only lymphadenopathy proved to be different between groups and occurred exclusively in five (15%) FIB patients (p=0.045). CT detection of interstitial change proved surprisingly poor, with positive and negative predictive values of 0.98 and 0.11, respectively. However, combining TLC <90% and interstitial change on CT proved the most accurate, returning positive and negative predictive values of 1.00 and 0.75, respectively.

No differences in underlying disease (p=0.716), conditioning protocols (p=0.497), total lymphoid irradiation (p=0.833) or type of stem-cell procedure (p=0.623) were evident between groups. 16 (27%) patients, of whom nine were in the FIB group, demonstrated no evidence of extrapulmonary GvHD. Although PPFE was present in 19 (39%) out of 49 patients assessed, no reliable risk factors for its development were apparent. Neither spirometry nor CT proved particularly discriminatory for PPFE, and it did not impact on the interval between HSCT and LTx (68 *versus* 74 months; p=0.56). By contrast LTx-free survival was significantly longer among FIB patients (66 *versus* 109 months; p=0.03).

Taken collectively, these results suggest that advanced noninfective lung complications of allogeneic HSCT, at the very least among patients amenable to LTx, demonstrate variable pathology beyond merely bronchiolitis obliterans and that interstitial involvement is common. Perhaps more importantly, these results highlight the limitations of current diagnostic criteria. In total, 24 (40%) out of 60 patients with end-stage lung disease failed to fulfil NIH clinical criteria. Whilst these represent a reasoned pragmatic attempt to harness reporting of pulmonary complications, they presume the presence of a purely obstructive lung disease both in terms of spirometry and imaging. The data presented appears to call this presumption into question with only six patients exhibiting isolated bronchiolitis obliterans. A clear clinical dichotomy relying on lung volumes and CT imaging could be distinguished.

Clearly the potential for selection bias within the cohort cannot be ignored, given the rigorous extrapulmonary criteria demanded of LTx recipients. Whilst this makes extrapolation of these findings difficult, it nonetheless allows objective questioning of a currently engrained model, encouraging reappraisal and perhaps triggering development of effective targeted treatment strategies. Its purpose is that of a catalyst for further studies involving unselected NIPC patients. These should ideally include longitudinal data, to better understand disease evolution.

Given the ever increasing rates of allogeneic stem-cell transplantation, the poor prognosis and lack of effective treatment of noninfectious pulmonary complications have the potential to become a considerable clinical problem for pulmonologists and haematologists alike. A more detailed understanding of the problem appears to be an important first step.

TABLE 1 Summary of patient demographics, treatment and associated extrapulmonary disease relating to stem-cell transplantation

Patient demographics	All	Phenotypes		p-value
		BO	FIB	
Subjects	60	26 (43%)	34 (57%)	
Male	35 (58%)	13 (50%)	23 (68%)	0.181
Age at diagnosis years	24.8 (13.6–35.8)	27.0 (19.4–35.1)	22.0 (6.7–33.2)	0.078
Age at HSCT years	25.8 (13.6–35.8)	29.0 (20.4–36.4)	22.4 (10.1–34.9)	0.074
Airway colonisation	23 (38%)	10 (38%)	13 (38%)	1.000
Pseudomonas aeruginosa	10 (17%)	4 (15%)	6 (18%)	
Aspergillus fumigatus	7 (12%)	4 (15%)	3 (9%)	
Never-smoker	51 (85%)	22 (85%)	29 (85%)	1.000
LTx-free survival months	75 (37–134)	66 (35–105)	109 (56–155)	0.030
Spirometry characteristics				
FEV_1% pred	18 (15–21)	18 (15–24)	18 (15–21)	0.824
FVC % pred	35 (23–48)	46 (31–53)	31 (19–44)	0.016
FEV_1/FVC %	42 (33–64)	35 (31–42)	56 (36–75)	0.008
TLC % pred[#]	102 (69–121)	118 (101–123)	74 (50–112)	0.004
CT features				
Air trapping	34 (57%)	17 (65%)	17 (50%)	0.305
Pulmonary fibrosis	29 (48%)	7 (27%)	22 (65%)	0.008
Emphysema	18 (30%)	6 (23%)	12 (35%)	0.403
Bronchiectasis	41 (68%)	15 (58%)	26 (76%)	0.253
Lymphadenopathy	5 (8%)	0	5 (15%)	0.045
Histology				
Bronchiolitis obliterans	55 (92%)	26 (100%)	29 (85%)	0.130
Pulmonary fibrosis	34 (57%)	0	34 (100%)	
Organising pneumonia	13 (22%)	5 (20%)	8 (24%)	0.760
Emphysema	9 (15%)	4 (10%)	5 (21%)	1.000
Bronchiectasis	19 (32%)	7 (28%)	12 (36%)	0.579
PPFE[¶]	19 (39%)	6 (23%)	13 (57%)	0.042
Underlying disease				0.716
AML	24 (40%)	10 (38%)	14 (40%)	
ALL	10 (16%)	4 (15%)	6 (18%)	
CML	13 (22%)	6 (23%)	7 (21%)	
CLL	1 (2%)	0	1 (3%)	
NHL	2 (3%)	1 (4%)	1 (3%)	
Hodgkin lymphoma	1 (2%)	0	1 (3%)	
Neuroblastoma	1 (2%)	1 (4%)	0	
MDS	2 (3%)	2 (8%)	0	
Non-malignant	6 (10%)	2 (8%)	4 (12%)	
Conditioning treatment				0.497
Non-myeloablative	1 (2%)	1 (5%)	0	
Reduced intensity	7 (13%)	3 (13%)	4 (13%)	
Myeloablative	44 (85%)	18 (82%)	26 (87%)	
TBI	28 (53%)	12 (54%)	16 (52%)	0.833
Drug exposition during HSCT induction therapy				
Busulphan	22 (37%)	10 (38%)	12 (35%)	0.873
Cyclophosphamide	34 (57%)	13 (50%)	21 (62%)	0.099
Fludarabine	10 (17%)	7 (27%)	3 (9%)	0.165
Melphalan	7 (12%)	4 (15%)	3 (9%)	0.694
GvHD prophylaxis				
Ciclosporine	50 (83%)	22 (85%)	28 (82%)	0.730
Steroid	48 (80%)	21 (81%)	27 (79%)	0.969
Mycophenolate	22 (37%)	13 (50%)	9 (26%)	0.271
Methotrexate	12 (20%)	3 (12%)	9 (26%)	0.149
Extrapulmonary GvHD				
Any	43 (72%)	18 (72%)	25 (74%)	0.829
Skin	27 (45%)	11 (42%)	16 (47%)	0.816
Gastrointestinal	14 (23%)	8 (31%)	6 (18%)	0.229
Ocular	21 (35%)	7 (27%)	14 (41%)	0.411
Mucosal	23 (43%)	8 (31%)	15 (44%)	0.166

Data are presented as median (interquartile range), unless otherwise stated. ALL: acute lymphoblastic leukaemia; BO: isolated bronchiolitis obliterans subgroup; FIB: mixed airway and interstitial disease subgroup; HSCT: haematopoetic stem cell transplantation; LTx: lung transplantation; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity; CT: computed tomography; PPFE: pleuroparenchymal fibroelastosis; AML: acute myeloid leukaemia; CML: chronic myeloid leukaemia; CLL: chronic lymphocytic leukaemia; NHL: non-Hodgkin lymphoma; MDS: myelodysplastic syndrome; TBI: total body irradiation; GvHD: graft-*versus*-host disease. [#]: data available in 31 patients (BO n=17, FIB n=14); [¶]: data available in 49 patients (BO n=26, FIB n=23).

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Interstitial lung disease is a common, largely unrecognised feature of pulmonary GvHD after stem cell transplant http://ow.ly/DWP4307mO3i

Mark Greer[1,2], Gerdt C. Riise[3], Lennart Hansson[4], Michael Perch[5], Pekka Hämmäinen[6], Antoine Roux[7], Sandrine Hirschi[8], Elodie Lhuillier[9], Martine Reynaud-Gaubert[10], Francois Philit[11], Johanna Claustre[12], Marc Stern[7], Jens Gottlieb[1,2] and Are M. Holm[13]
[1]Hanover Medical School, Hanover, Germany. [2]Biomedical Research in End-Stage and Obstructive Lung Disease (BREATH), German Center for Lung Research (DZL), Hanover, Germany. [3]Sahlgrenska University Hospital, Gothenburg, Sweden. [4]Skåne University Hospital, Lund, Sweden. [5]Rigshospitalet, Copenhagen, Denmark. [6]Helsinki University Hospital, Helsinki, Finland. [7]Hospital Foch, Suresnes, France. [8]Strasbourg University Hospital, Strasbourg, France. [9]Hospital Bichat, Paris, France. [10]University North Hospital, Marseille, France. [11]Hospital Louis Pradel, Bron, France. [12]CHU Grenoble, Clinique Universitaire de Pneumologie, Grenoble, France. [13]Oslo University Hospital Rikshospitalet, Oslo, Norway.

Correspondence: Mark Greer, Hanover Medical School, Carl-Neuberg-Straße 1, 30625 Hanover, Germany.
E-mail: greer.mark@mh-hannover.de

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