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Lung biopsy findings and pulmonary function in children after allogeneic hematopoietic stem cell transplantation

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BACKGROUND: Pulmonary complications are a major cause of morbidity after allogeneic hematopoietic stem cell transplantation (HSCT). Late-onset non-infectious pulmonary complications (LONIPCs), especially bronchiolitis obliterans syndrome (BOS), are difficult to diagnose, particularly in paediatric patients.
METHODS: In this retrospective single-center study, 14 of 325 paediatric HSCT recipients (4.3%) who developed severe pulmonary symptoms between 1999 and 2016 were analyzed. Lung biopsies were correlated with high-resolution computed tomography (HRCT) and pulmonary function tests (PFTs). Fourteen postmortem biopsies from HSCT patients without pulmonary symptoms served as controls.
RESULTS: Histology showed BOS in eight patients, cryptogenic organizing pneumonia (COP) in three, and interstitial fibrosis in three. None of the controls had findings suggestive of LONIPCs. All patients with BOS exhibited obstructive spirometry results, while restrictive changes occurred in COP and fibrosis. HRCT findings, including bronchial wall thickening and dilation, were frequent but non-specific. The incidence of LONIPCs and BOS was 4% and 2%, respectively.
CONCLUSIONS: BOS was the most common late-onset pulmonary complication after paediatric HSCT. Obstructive PFT changes correlated well with histological BOS, whereas HRCT findings lacked specificity. Regular pulmonary function monitoring appears more reliable than imaging for early detection and may help prevent progression to irreversible lung disease.

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IMPACT:

- This study highlights the diagnostic value of combining functional and histological assessment in children after HSCT.
- Underscores the limitations of HRCT in detecting early BOS.
- Supports routine pulmonary function surveillance as a non-invasive strategy to improve long-term outcomes.

INTRODUCTION

Pulmonary complications affect over 30% of allogeneic hematopoietic stem cell transplant (HSCT) recipients.[1] Pulmonary complications are divided into infectious and non-infectious and into early onset and late onset, depending on the time elapsed after HSCT. Late-onset non-infectious pulmonary complications (LONIPCs) develop beyond three months post-HSCT, and their incidence is 10%–25% in paediatric HSCT recipients.[2–4] The overall survival of patients with LONIPCs is significantly lower than that of patients without LONIPCs (28%–37% and 73%–87%, respectively).[2,3]

LONIPCs are difficult to recognize, and they are often diagnosed when respiratory symptoms, such as cough, difficulty in breathing or dyspnoea, occur. All forms of LONIPCs have been suggested to be caused by alloimmune reactions against pulmonary structures, but the only entity recognized as chronic is lung graft-versus-host disease (GvHD), and the most frequently diagnosed LONIPC in HSCT patients is bronchiolitis obliterans (BOS).[2,5–9] Other LONIPCs include cryptogenic organizing pneumonia (COP), formerly called bronchiolitis obliterans organizing pneumonia, and interstitial lung diseases, such as pleuroparenchymal fibroelastosis.[9,10]

Despite the many changes in conditioning regimens, donor selection and the use of antithymocyte globulin, the incidence of BOS remains high, affecting about 9% of allogeneic HSCT recipients.[11] For many years, lung biopsy has been considered the gold standard of diagnosis.[7] The histological picture of BOS is unclear. The findings indicative of BOS are comparable after lung transplantation and HSCT and include a thickened basement membrane in the airways, fibrosis around the bronchiole and in the alveolar septae, lymphocytic infiltrates, vanishing airways, and chronic vasculopathy in arteries and veins in varying degrees.[12]

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The National Institute of Health (NIH) consensus criteria were developed to help in the diagnosis of GvHD of the lungs, and modifications to the criteria have been proposed to improve their sensitivity to catch the disease.[8,10,13–17]

This study aimed to enlighten the histological findings of patients with severe lung symptoms after allogeneic HSCT and how these findings correlate with high-resolution lung computer tomography (HRCT) and pulmonary function tests (PFTs), with a special focus on LONIPCs.

MATERIALS AND METHODS

This retrospective study was performed at Helsinki University Hospital, Children and Adolescents, Finland. Out of 325 paediatric HSCT recipients, we identified 14 (4.3%) with severe pulmonary symptoms and lung biopsies taken during 1999–2016. PFTs and HRCT images were re-analyzed from children with lung biopsy.

As controls, we collected postmortem lung biopsies from 14 children who underwent allogeneic HSCT for malignant underlying disease and had no pulmonary symptoms. Eight patients with pulmonary symptoms were evaluated for hypoventilation and ventilation–perfusion mismatch in polysomnography in our earlier study.[18] Here, we present the histological picture of these eight patients and six other patients.

Ethical approval was obtained from the Ethics Committee of Helsinki University Hospital.

Clinical data

Clinical data were collected from the local HSCT database and patient charts. Information included patient demographics and underlying disease characteristics, HSCT characteristics with information about conditioning regimen and medications used, donor and graft characteristics, engraftment, presence of infections and viral findings and acute and chronic GvHD data. Lung symptoms registered were cough, shortness of breath and difficulty in breathing without any infectious agent present. Total body irradiation (TBI) was fractionated in 2 Gy fractions, two fractions per day. Lung shielding capping the lung irradiation dose at 8 Gy was used in 6/14 patients with lung symptoms and 8/14 without lung symptoms.

Pulmonary function

As part of routine follow-up after HSCT, pulmonary function was assessed by spirometry before transplantation, at 6 months, 1 year, and annually up to 5 years post-transplantation, with additional assessments performed as needed in symptomatic children during this period and thereafter. PFT results at the time of lung biopsy were collected from patients with lung symptoms. We included digitised original spirometry flow-volume curves, forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1). The HRCT images at the time of biopsy were analyzed by a radiologist (LM) blinded to the clinical history. The presence of a mosaic pattern, bronchial wall thickening, bronchial dilation, ground glass opacity and air trapping were recorded in six different lung areas. A full score ranged from 0 (no lobe affected) to 6 (all lobes affected). All histopathological samples were re-analyzed by two experienced paediatric pathologists (JL, RK) blinded to the clinical history. Findings on the bronchial wall and bronchial inflammation, bronchial and alveolar epithelium, emphysema, macrophages, interstitial fibrosis, interstitial inflammation, arteries, arterial endothelium, muscle layer, venae and capillaries were reported. Viral and/or bacterial findings were also recorded.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics version 25 (Armonk, IL). Non-parametric tests were used. The demographic data were compared between groups by applying Fisher's exact test, chi-square test and two-sample z-test. Between-group analyses were performed using the Mann–Whitney *U*-test. Repeated test results were verified using the paired-sample Wilcoxon signed-rank test. *P* values of 0.05 or below were considered significant.

RESULTS

The demographic data of patients with and without lung symptoms are presented in Table 1. Patients with lung symptoms had more chronic GvHD, CMV infections and matched unrelated donors used as the graft source. No differences were found in the use of a conditioning regimen, including TBI and lung shields, incidence of respiratory viral infections, GvHD prophylaxis or acute GvHD grade.

Table 1. Demographic data of patients with and without lung symptoms.

Charasteristic	Lung symptoms group $N = 14$	No lung symptoms group $N = 14$	*P* value
Median age at HSCT (IQR)	6.8 (5-10.9)	7.6 (5.1–9.3)	0.8
Sex (%)			0.6
Female	4 (29%)	2 (14%)	
Male	10 (71%)	12 (86%)	
Pretreatment (%)			1.0
Cyclophosphamide-based	8 (57%)	8 (57%)	
Cytarabine-based.	6 (43%)	5 (36%)	
Other	0	1 (7%)	
TBI (%)			0.17
10 Gy	9 (69%)	5 (36%)	
>10 Gy	4 (31%)	7 (50%)	
Other		2 (14%)	
Lung shielding during TBI (%)	6 (43%)	8 (57%)	0.45
Donor (%)			0.02
- MatchedURD	9 (64%)	12 (86%)	
- Matched Family	5 (36%)	2 (14%)	
GvHD prophylaxis (%)			0.48
Cyclosporine based	14 (100%)	12 (86%)	
Other	0	2 (14%)	
Viral infections			
CMV	12 (86%)	4 (29%)	0.002
Adeno	1 (7%)	5 (36%)	0.17
Resp	4 (29%)	8 (57%)	0.13
Acute graft-versus-host-disease(%)			0.4
Grade 0-1	6 (43%)	3 (21%)	
Grade 2–4	8 (57%)	11 (79%)	
Chronic GvHD other than lungs	8 (57%)	2 (14%)	0.018

HSCT hematopoietic stem cell transplantation, *TBI* total body irradiation, *URD* unrelated donor, *CMV* cytomegalovirus, Resp respiratory viruses in the nasopharyngeal secrete, *GvHD* graft-versus-host disease.

The lung biopsy findings in 14 children with lung symptoms and 14 children without lung symptoms are presented in Table 2. Eight children with severe lung symptoms had a histological finding of BOS, three had COP, and three had interstitial fibrosis. None of the patients without lung symptoms had histological findings suggestive of BOS, COP or interstitial fibrosis. The most common finding was diffuse alveolar damage (n = 8), along with aspergillus infection in one patient. See Fig. 1 for the histological findings in a patient with COP and a patient with BOS.

PFTs at the time of biopsy were evaluated in patients with lung symptoms. For detailed PFT and HRCT findings according to biopsy results, see Table 3. PFT data were available in 11/14

Table 2. Biopsy findings of patients with and without lung symptoms.

#	Grp.	Biopsy type	Bronchial wall	BWLI	Bronchial epithelium	Interstitial fibrosis	Arteries
1	LS	L	Thickening, obliteration	+++	Proliferated, eroded	Fibrotic foci, +++	Focally thickened, plicated
2	LS	L	Thickening, obliteration	++	Eroded	Fibrotic foci, +++	Focally thickened, plicated
3	LS	L	Submucosal thickening	+	Eroded	No	Focally thickened, plicated
4	LS	L	Normal	No	Focally eroded	Focal, subpleural fibrosis, ++	Focally thickened, plicated and oblitared
5	LS	L	Thickening, obliteration	++	Eroded	No	Normal
6	LS	L	Thickening, obliteration	++	Proliferated, inflammation	No	Normal
7	LS	L	Thickening, obliteration, necrosis	+	Eroded. Squamous cell metaplasia, organizing hyaline membranes	Diffuse fibrosis, +++	Onion-like intima thickening, plicated wall
8	LS	L	Bronchi and bronchioles destroyed	NA	Bronchi and bronchioles destroyed	Nodular fibrosis, +++	Normal
9	LS	A	Thickening, hyaline membranes	+	Eroded, metaplasia, hyaline membranes	Diffuse fibrosis, +	Normal
10	LS	L	Fibrotised, missing	NA	Fibrotised, missing	Focal fibrosis, +	Normal
11	LS	L	NA	NA	NA	Focal, subpleural fibrosis, ++	Normal
12	LS	L	Thickening, obliteration	+++	Hyperplastic, papillary proliferation	Diffuse fibrosis, +++	Normal
13	LS	L	Few bronchi	No	Eroded	Fibrosis, +	Intimal thickening
14	LS	L	NA	No	Eroded	Diffuse, +++	Normal
15	WLS	A	Normal, focal thickening	No	Normal	No	Intimal thickening
16	WLS	A	Normal	No	Squamous cell metaplasia	Diffuse fibrosis, +++	Onion-like intima thickening
17	WLS	A	Normal	No	Normal	NA	NA
18	WLS	A	Normal	No	Hyaline membranes	NA	NA
19	WLS	A	Normal	No	Epithelial metaplasia, intrabronchial hemorrhage, epithelia destroyed	No	NA
20	WLS	A	Normal	No	Hyaline membranes	No	Normal
21	WLS	A	Normal	No	NA	No	Normal
22	WLS	A	Normal	No	Normal	No	Normal
23	WLS	A	Normal	No	Hyaline membranes	No	NA
24	WLS	A	Normal	No	Normal	No	Full of bacteria
25	WLS	A	Normal	No	Normal	No	Normal
26	WLS	A	Normal, peribronchial hemorrhage	No	Hyaline membranes, bacterial mass	No	Normal
27	WLS	A	Normal	No	Normal	No	Focally thickened, plicated wall
28	WLS	A	Thickening	+	Eroded, focal squamous cell metaplasia	No	Normal, fungal mass

#patient nro, *Grp* patient group, *BWLI* Bronchial wall lymphocytic infiltration, *NA* not available, *LS* lung symptoms, *WLS* without lung symptoms, *L* lung, *A* autopsy.

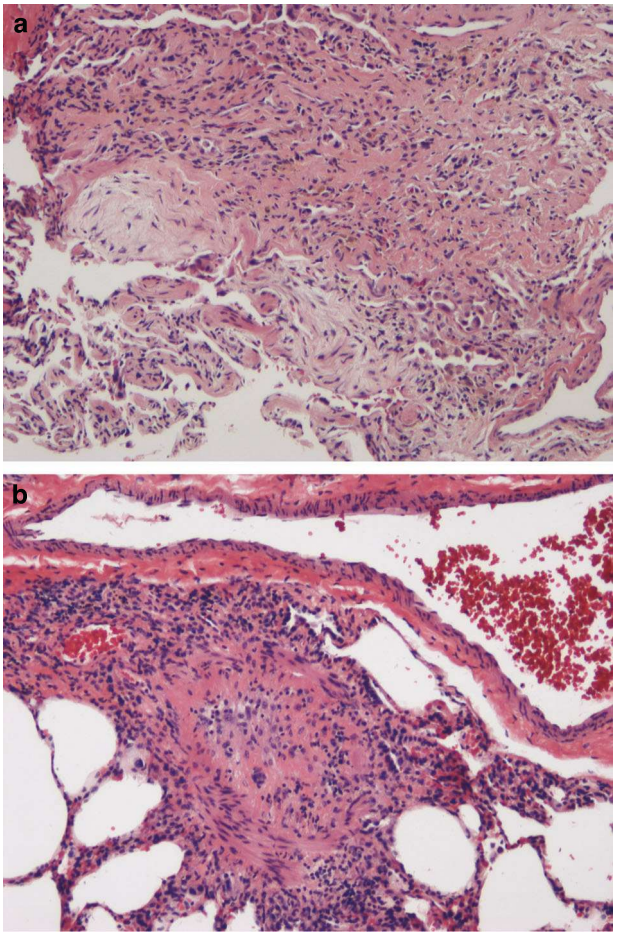

Fig. 1 The histological hallmark of cryptogenic organizing pneumonia (COP) is a fibroblast focus. Fibroblast foci are variably dense proliferative aggregates of fibroblasts embedded in a ground substance of a loose collagen matrix. These alveolar filling processes can be seen extending into or from terminal bronchioles, and they are repair process following injury at the level of terminal bronchioles and alveoles. **a** On the other hand, obliterative bronchioliltis (OB) is characterized by fibrous proliferation at the bronchial level resulting in obstruction and complete obliteration of small muscular airways leading to the clinical entity referred ad bronchiolitis obliterans syndrome (BOS). BOS is related to immune mediated injury of bronchiolar epithelium in the context of chronic lung transplant rejection or graft-versus host disease in bone marrow transplants **b**.

patients. Three patients had missing PFTs because of their young age ($n = 2$) and poor clinical condition ($n = 1$). Patients with lung biopsies had a median FVC and FEV1 of 53%/-3.8 SD (interquartile range [IQR] 37.5%–63%/-4.7 - -2.4 SD) and 33%/-4.6 SD (IQR 31%–59%/-4.7 - -2.6 SD), respectively.[19] Patients with lung symptoms had a median FEV1/FVC of 0.9/-1 SD (IQR 0.7–1.1/-2.9 - 1.0 SD).[19] Only two patients had FEV1/FVC < 0.7 or < -2 SD, both having a histological diagnosis of BOS. All patients with a histological diagnosis of BOS had obstructive spirometry curves (Fig. 2). Obstruction was also found in two patients with a histological diagnosis of interstitial fibrosis. A restrictive spirometry finding was observed in patients with COP ($n = 1$) and interstitial fibrosis ($n = 1$).

HRCT was conducted on 12/14 patients with lung symptoms. The HRCT findings were bronchial wall thickening ($n = 11$), bronchial dilation ($n = 9$), mosaic pattern ($n = 9$), ground glass opacity ($n = 4$) and air trapping ($n = 4$). The findings related to BOS, bronchial thickening and air trapping were found in 3/8 patients with a histological diagnosis of BOS. Bronchial wall dilation with bronchial wall thickening was observed in 6/8 patients with BOS.

Table 3. Histological diagnosis, PFT and HRCT findings in patients with lung symptoms.

Patient no.	*Dg*	*PFT*	*HRCT*	
			Bronchial wall thickening	*Air trapping*
1	BOS	Obstructive	Yes	No
2	BOS, fibrosis	Obstructive	Yes	No
3	BOS, air trapping	Obstructive	Yes	No
5	BOS	Obstructive	Yes	No
9	BOS		NA	
10	BOS	Obstructive	Yes	Yes
11	BOS	Obstructive	Yes	Yes
12	BOS, interstitial inflammation	Obstructive	Yes	Yes
6	COP	Restrictive	Yes	No
7	COP	NA	No	No
8	COP, fibrosis	NA	Yes	No
4	Subpleural fibrosis	Obstructive	Yes	No
13	Congestion, fibrosis	NA	NA	
14	Chr. interstitial fibrosis	Restrictive	Yes	Yes

Dg diagnosis, *PFT* pulmonary function test, *HRCT* high-resolution lung computer tomography, *BOS* bronchiolitis obliterans, *COP* Organizing pneumonia, *NA* not available.

DISCUSSION

Severe lung alloreactivity is a bronchial disease, and its diagnosis involves the use of various modalities, such as biopsy, PFT and HRCT. In biopsies, BOS has been recognized as a manifestation of lung symptoms related to alloreactivity. All our patients with BOS exhibited obstructive pulmonary findings consistent with this diagnosis. In our study, the incidence of LONIPCs was 4% and that of BOS was 2%, whereas in other paediatric studies, the corresponding figures were 10% and 2%–8%, respectively.[2,4,20–23] This one-center series of 14 out of 325 paediatric HSCT patients with severe lung symptoms showed that the histological findings were different between patients with and those without lung symptoms after HSCT.

BOS was the most common diagnosis in patients with lung symptoms (Table 3). The histological finding of BOS is recognized as chronic GvHD of the lungs, but alloimmunity may play a role in other entities, such as COP and interstitial fibrosis.[2,9] In Meignin et al.'s study, the histological finding of BOS included totally obstructed bronchioles with bronchiectasis.[9] This is supported by our finding that patients with BOS had bronchial wall thickening and bronchial dilation. Meignin et al. hypothesised that obstruction of distal bronchioles leads to bronchiectasis/bronchial dilation in proximal bronchioles.[9] Examining serial sections using the same procedure should be investigated in the future.[9] Recent studies have suggested that COP, pleuroparenchymal fibroelastosis and other interstitial lung diseases could be the early signs of BOS.[9] According to Holbro et al., BOS has been described as comprising

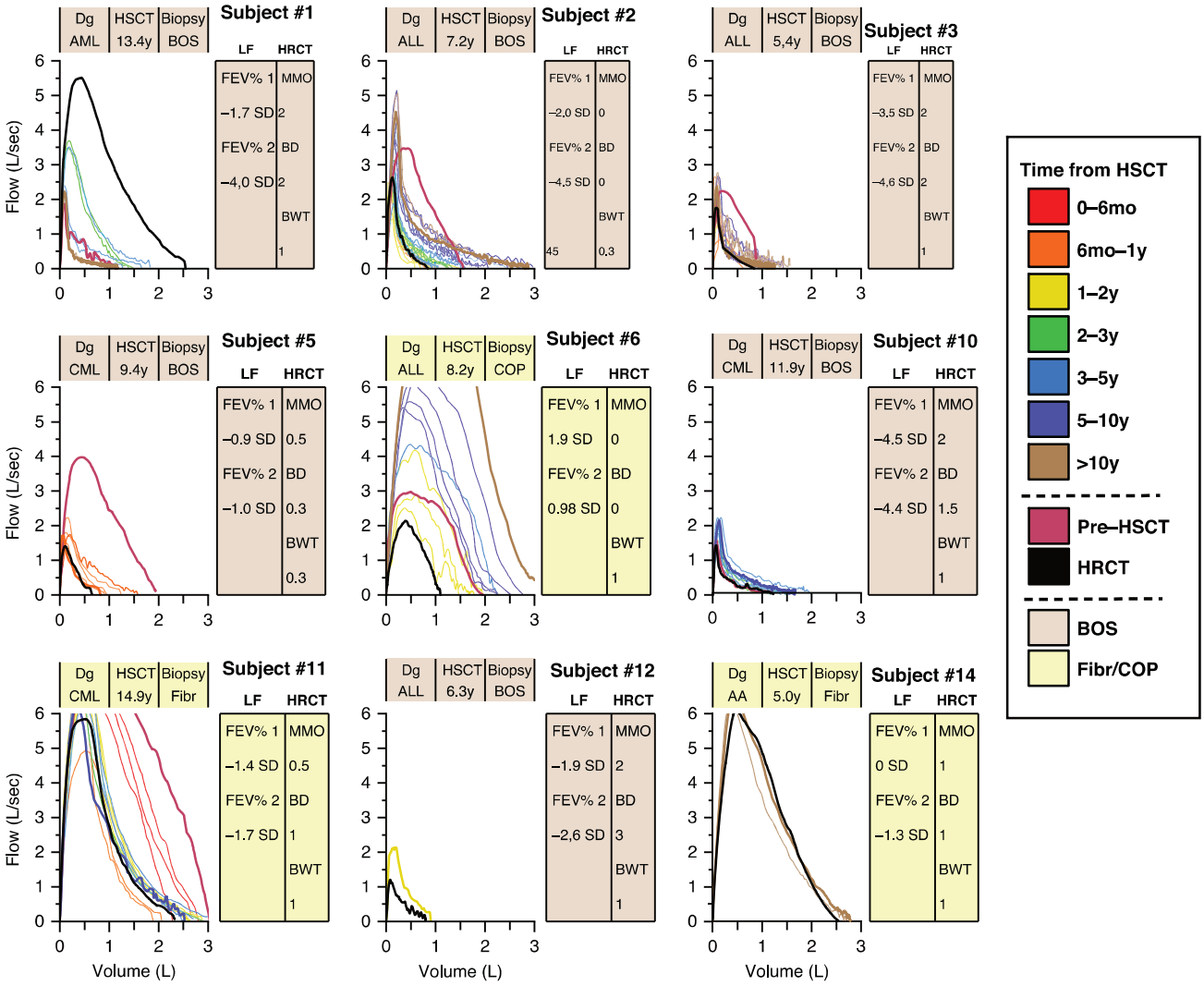

Fig. 2 Individual spirometry and lung imaging results. Children 1, 2, 3, 5, 10 and 12 had lung histology consistent with obliterative bronchiolitis (BOS), with spirometry findings supporting (most likely dynamic) small airway obstruction. In the spirometry panels, the curve obtained closest in time to the lung biopsy is indicated by a thicker black line. In each figure, the right panel shows FEV1/FVC (%) expressed as standard deviations from predicted values, along with a summary of HRCT findings. PFT data missing from three patients and in two patients the flow-volume spirometry curve could not be regenerated. AA, aplastic anemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; BD, bronchial dilation; BOS, bronchiolitis obliterans syndrome; BWT, bronchial wall thickening; CML, chronic myeloid leukemia; Dg, diagnosis; FEV%1, spirometry closest to lung biopsy; FEV%2, latest available spirometry (<21 years); Fibr, interstitial fibrosis; HRCT, high-resolution computed tomography; HSCT, allogeneic hematopoietic stem cell transplantation; LF, lung function testing; MMO, mosaic attenuation pattern.

two distinct histological patterns: constrictive bronchiolitis obliterans and lymphocytic bronchiolitis.[24] Lymphocytic bronchiolitis has been proposed to represent an earlier stage in the pathological process leading to BOS.[24–27] In the studies of Holbro et al. and Meignin et al., no clear correlation was observed between the hypothesised pathological stages of BOS and findings in radiology or PFTs.[9,24] Lymphocytic bronchiolitis appears to respond better to treatment and has been associated with a more favourable long-term prognosis than constrictive bronchiolitis obliterans, suggesting that recognition and treatment of these early inflammatory changes may be clinically relevant.[24] In our study, lymphocytic infiltration was a consistent histological finding in patients with both BOS and COP. While our data does not allow conclusions regarding a causal or temporal relationship between these conditions, the presence of lymphocytic inflammation in both groups supports the need for further studies exploring early inflammatory lung changes after transplantation and their potential role in the development of BOS.

In patients without lung symptom infections and acute reactions related to a preparative regimen and radiation, diffuse alveolar haemorrhage is the major cause of mortality.[28]

Patients with BOS, COP and pulmonary fibrosis had a clear decrease in lung function, with a mean FEV1 of 33%/-4.6 SD. All our patients with a histological diagnosis of BOS exhibited obstructive features on flow-volume spirometry curves (Fig. 2). In addition, obstructive findings were found in patients with fibrotic histology. None of the patients diagnosed with BOS demonstrated restrictive spirometry results, thus implying that if post-HSCT and PFT follow-up reveals a restrictive spirometry outcome, it indicates the need to consider diagnoses other than BOS. Conducting follow-up PFTs in children presents challenges due to their inability to reliably perform testing before the age of seven, as seen in our patients. In these cases, polysomnography emerged as a feasible non-invasive method to differentiate patients with BOS from other LONIPCs.[18]

The 2005 and 2014 NIH criteria failed to catch BOS early, and studies have shown that close serial monitoring of FEV1 decline is

better than the NIH criteria.[5,8,16,29,30] An update in the NIH consensus criteria in 2020 stated that a > 10% decline in FEV1 from pre-HSCT values is indicative of BOS or other lung complications.[31] The requirement of FEV1/FVC < 0.7 in the 2014 NIH consensus criteria can lead to misdiagnoses, especially in children.[16,31] In BOS patients, FVC may decline concurrently with a decline in FEV_1, implying mixed obstructive/restrictive processes.[15,31] This was observed in our patients with a histological diagnosis of BOS, with a median FEV1/FVC of 0.9/-1 SD (IQR 0.7–1.1/-2.9 - 1.0 SD).

In adults, HRCT is considered sensitive for diagnosing BOS. Detecting air trapping is challenging in the paediatric population, with a demand for inspiratory and expiratory phases. According to the 2014 modified NIH criteria, air trapping is no longer mandatory.[16] In our study, the HRCT findings were not specific to BOS. HRCT is a useful tool for detecting lung complications, but, as our study suggests, the signs of airway disease in HRCT are too unspecific to use in diagnosing BOS. This is supported by the literature.[1] Lung function tests with a persistent decrease in FEV1 are considered a better marker of BOS than radiographic methods.[5,29,32]

The trend in diagnosing BOS is moving from biopsy to PFT follow-up. PFT is non-invasive, affordable and easy to conduct. The role of biopsy for pulmonary function in the long-term follow up of patients with LONIPCs is unclear.[14] According to the updated 2020 NIH criteria, the presence of an infective agent, along with a decline in FEV1, should be considered high risk for BOS, and intense pulmonary follow-up is needed.[31] Studies have shown that lung biopsies are required when the treatment of infections does not improve patients' condition and when diagnosing non-infectious complications.[11,33,34] In these situations, a biopsy leads to treatment changes more often than bronchoalveolar lavage.[33]

The limitations of this study include missing PFT ($n = 3$) and HRCT ($n = 2$) results from patients with lung symptoms. Given the limited cohort size, even a small number of missing data points may meaningfully affect the analyses and the observed correlations and should be considered when interpreting the results. Postmortem biopsies served as control samples, which could not represent an ideal control population. As biopsies could not be conducted on individuals with mild or no symptoms, comparisons had to rely on autopsy data.

There are a limited number of studies on paediatric patients with lung biopsies after HSCT. We were able to compare the histological findings with postmortem biopsies of patients with allogeneic HSCT. The histological picture of LONIPCs, especially in BOS, is not clear, and only a few studies have presented pathological findings. We correlated the histological findings with the PFT and HRCT findings to increase our understanding of this rare complication. In sum, the current study and our previous study about sleep-related breathing disorders in patients with BOS clarify the interpretation of PFT and suggest new ways to separate patients with possible GvHD of the lungs from those with other pulmonary problems.[18] This study helps to understand PFT findings and guide decision-making in proceeding with biopsies.

In conclusion, this study shows that the PFT findings correlate well with BOS in histological samples. To catch GvHD of the lungs in the early phases and possibly prevent the development of BOS, intense pulmonary function follow-up and treatment should start as soon as PFT shows an obstructive decrease without acute infection. More studies are needed to determine whether early treatment of LONIPCs can prevent the development of BOS.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

E.M.U. was responsible for designing the study, collecting and analysing data, statistical analysis, creating tables and writing the first draft of the manuscript. T.K. analyzed the pulmonary function tests and revised the manuscript. L.M. analyzed the high-resolution computed tomography images of the lungs. J.L. and R.K. examined lung biopsies. M.K. revised the manuscript. M.T. designed the study and revised the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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