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CASE REPORT

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# Tracheobronchomalacia following allogeneic haematopoietic stem cell transplantation

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## Abstract

Tracheobronchomalacia (TBM) occurs due to the weakening of cartilaginous part of the trachea, resulting in compromised airway function and leading to symptoms such as dyspnea, cough, and inability to clear secretions. Bronchiolitis obliterans syndrome (BOS) is the most prevalent late noninfectious pulmonary complication in patients who underwent allogeneic haematopoietic stem cell transplantation (HSCT). Therefore, patients experiencing progressive dyspnea and chronic cough after allogenic HSCT, with new obstructive pattern on pulmonary function test, are typically diagnosed with post-transplant BOS. However, it is important to note that TBM can also manifest as an obstructive defect pattern on pulmonary function test. Tracheomalacia has been reported as a rare complication of allogenic stem cell transplantation. We present two patients who developed TBM following allogeneic HSCT and were initially treated for post-transplant BOS but did not experience symptom improvement. However, after treatment with continuous positive airway pressure, their symptom subsided.

**KEYWORDS**
allogeneic haematopoietic stem cell transplantation, excessive central airway collapse, tracheobronchomalacia, tracheomalacia

## INTRODUCTION

Tracheobronchomalacia (TBM) occurs due to the weakening of cartilaginous part of the trachea, resulting in compromised airway function and leading to symptoms such as dyspnea, cough, and an inability to clear secretions.[1] Tracheomalacia has been reported as a rare complication associated with allogenic haematopoietic stem cell transplantation (HSCT).[2]

Bronchiolitis obliterans syndrome (BOS) is recognized as the most prevalent late noninfectious pulmonary complication in patients who have undergone allogeneic HSCT.[3,4] Therefore, individuals manifesting progressive dyspnea and chronic cough subsequent to allogeneic HSCT, in conjunction with newly identified obstructive patterns on pulmonary function tests, are commonly diagnosed with post-transplant BOS.

We present two patients who developed TBM following allogeneic HSCT. Initially, our patients were diagnosed with BOS based on the 2014 National Institutes of Health (NIH) chronic graft-versus-host disease (GVHD) diagnostic criteria for BOS.[5] However, despite receiving treatment for BOS, the patients' symptoms persisted. It is noteworthy that TBM can also manifest as an obstructive defect pattern and expiratory air trapping, as seen in diagnostic criteria for BOS. Further investigation revealed that the lack of symptom improvement was attributed to the presence of concomitant TBM.

## CASE REPORT

### Case 1

A 60-year-old male with hypertension, diabetes mellitus, and stage IIIB chronic kidney disease was diagnosed with myelodysplastic syndrome with myelofibrosis in August 2011 at the age of 49. Subsequently, he underwent allogeneic HSCT from a matched sibling donor in March 2012. Notably, the baseline pulmonary function test (PFT) conducted for pre-transplant evaluation in 2012 showed normal respiratory function.

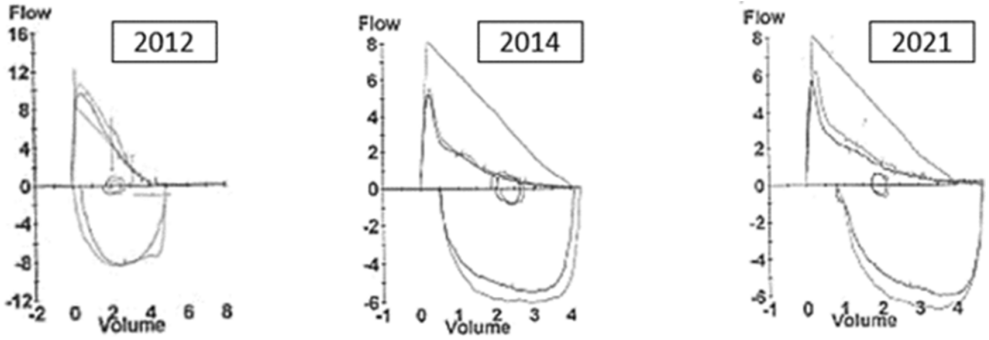


**FIGURE 1** Chronological change of flow volume loop in 2012, 2014, and 2021.

Two years after allogeneic HSCT, he developed chronic cutaneous GVHD, confirmed by biopsy as acute interface dermatitis, and was treated with prednisolone and tacrolimus. During that period, he began experiencing dyspnea on exertion. In 2014, his pulmonary function test revealed moderate obstructive defects, indicated by a reduction in the FEV1/FVC ratio to 0.44 and a post-bronchodilator FEV1 of 2.13 L (65%). High-resolution chest computer tomography showed expiratory air trapping without detectable emphysematous lung changes. Subsequently, a diagnosis of post-transplant BOS was established, leading to the initiation of a therapeutic regimen comprising fluticasone, azithromycin, and montelukast (FAM regimen) in conjunction with an inhaled long-acting beta2 agonist. Despite the treatment, his dyspnea symptoms persisted and worsened. He was readmitted four times between 2022 and 2023 due to worsening dyspnea on exertion and hypoxic respiratory failure, requiring intubation. His clinical condition improved with the application of positive pressure. However, upon withdrawing the positive pressure, his dyspnea symptoms worsened, accompanied by expiratory rhonchi observed over the intrathoracic trachea and main bronchi.

His post-bronchodilator FEV1 declined over time, decreasing from 4.01 L (119%) in 2012 to 2.13 L (65%) in 2014 and maintaining at 65% in 2021. The flow-volume loop comparison between 2014, 2015, and 2021 demonstrated a gradual increase in the degree of obstructive defect with a biphasic pattern on the flow-volume loop, reflecting a sudden disruption of airflow at the beginning of expiration (Figure 1). Additionally, high-resolution computed tomography (HRCT) of the chest revealed the collapse of the anterolateral wall of the trachea by more than 70% during the dynamic expiration phase. Consequently, a diagnosis of TBM was established, and the patient's symptoms improved after treatment with continuous positive airway pressure (CPAP). Although the reference standard for diagnosis of TBM is flexible dynamic bronchoscopy, we did not perform the procedure due to unstable patient's condition. Following the use of CPAP, the patient did not require admission due to respiratory failure again. Additionally, the patient reported a decrease in dyspnea.

## Case 2

A 57-year-old female, diagnosed with acute myeloid leukaemia, underwent allogeneic HSCT in December 2018. Preceding the transplantation, the patient's pulmonary function test revealed normal findings, characterized by a post-bronchodilator FEV1/FVC ratio of 0.79 and a post-bronchodilator FEV1 of 1.97 (92%).

In July 2019, she developed chronic cutaneous GVHD involving the skin and eyes. The prescribed treatment included prednisolone and cyclosporin. During that period, the patient experienced worsening symptoms, including progressive dyspnea, chronic dry cough, and exercise intolerance. The post-bronchodilator FEV1/FVC ratio decreased to 0.51, and FEV1 dropped to 1.18 (55%) with a biphasic pattern on the flow volume loop (Figure 2A). She was diagnosed with post-transplant BOS and received treatment with montelukast, fluticasone, and azithromycin. However, her symptoms did not improve. The obstructive defect persisted over time, with the latest FEV1/FVC ratio recorded at 0.55 and a post-bronchodilator FEV1 of 1.11 (52%) in February 2023. HRCT of the chest revealed a decreased cross-sectional area of the intrathoracic trachea, main bronchi, and bronchus intermedius over time (Figure 2B,C). Flexible optic bronchoscopy confirmed severe TBM, and the patient's symptoms improved after the application of CPAP at a level of 12 cmH2O. We determined the CPAP levels through titration, adjusting until the central rhonchi disappeared. After using CPAP, the patient reported reduced dyspnea and improved exercise tolerance.

## DISCUSSION

Herein we reported two cases of TBM following allogenic HSCT. Both cases presented with chronic GVHD and BOS. However, despite treating BOS, the patients' symptoms did not improve. There are differences in the nature and management between TBM and BOS. TBM is characterized by a loss of cartilaginous integrity of the trachea or bronchi.[6] TBM is caused by the pathological collapse of airway lumen at the anterolateral wall, resulting in symptoms such as

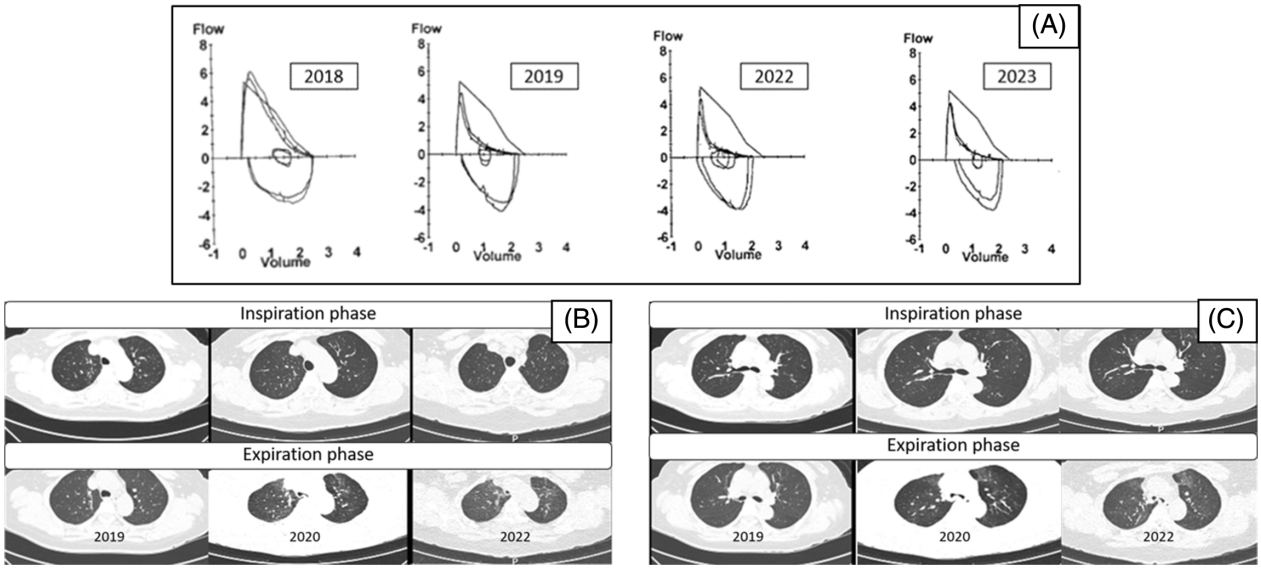


**FIGURE 2** (A) Chronological change of flow volume loop in 2018, 2019, 2022, and 2023. (B) High resolution computer tomography of the chest showing progression of anterolateral wall of tracheal collapsing leading to narrowing of airway lumen during expiration phase. (C) High resolution computer tomography of the chest showing progression of anterolateral wall of tracheal collapsing leading to narrowing of airway lumen during expiration phase.

intractable cough, wheezing, dyspnea, and recurrent bronchitis or pneumonia.[7,8] In contrast, BOS is the most prevalent late noninfectious pulmonary complication in patients who underwent allogeneic HSCT.[3,4] BOS induces progressive fibrosis and cicatrization of the small airways.[9] Consequently, BOS is characterized by a progressive obstructive ventilatory defect.[10]

BOS is the primary diagnostic manifestation of pulmonary chronic GVHD. According to the 2014 NIH chronic GVHD,[5] the diagnostic clinical criteria for BOS in patients who had GVHD are as follows: (1) FEV1/FVC <0.7 or the 5th percentile of predicted, (2) FEV1 < 75% of predicted with ≥10% decline over less than 2 years, (3) Absence of infection in the respiratory tract, and (4) evidence of air trapping by expiratory CT or small airway thickening or bronchiectasis by high-resolution chest CT or evidence of air trapping by PFT. Both of our patients fulfilled the diagnostic criteria for BOS. However, it is crucial to note that patients with TBM can also exhibit characteristics aligning with the criteria used to diagnose BOS. In our case reports, both patients initially received a bronchodilator and FAM regimen as the standard treatment for BO; however, their clinical condition did not improve. After re-evaluating, we found that the patients had concomitant TBM, and their symptoms improved with CPAP. Therefore, when patients with GVHD present with a new obstructive defect, physicians must carefully consider the possibility of TBM as well.

The pathophysiology of BOS following HSCT is not well understood. There is evidence that alloimmunity causes BOS.[9] The presence of neutrophils, plasma cells, and lymphocytes on lung biopsies indicates that donor immune cells are involved in lung damage.[9,11] Therefore, the pathophysiology of TBM in our patients after HSCT might be explained by inflammation of cartilage from an alloimmune reaction. Consequently, we hypothesized that chronic GVHD can also cause TBM. However, we cannot ascertain whether TBM results directly from GVHD or occurs secondarily to BOS, as obstructive airway disease can also lead to TBM. Aging can also contribute to TBM, but based on the HRCT chest findings, we observed progressive TBM occurring within a short period of time after allogeneic HSCT. This suggests that TBM is more likely due to the disease rather than aging.

The spirometry results in patients with TBM can exhibit various patterns, including a normal flow-volume loop, notching of the flow-volume loop, an oscillation pattern, and a biphasic pattern.[12] The biphasic pattern is marked by a sudden and significant drop in airflow at the beginning of expiration, followed by a plateau of low flow.[6] Our cases illustrate a distinctive biphasic pattern on the flow-volume loop during expiration, which is considered one of the hallmarks of TBM.

There are other treatment options for TBM, including stents or surgical interventions. Silicone Y stents have demonstrated improvement in symptoms and quality of life; however, they are associated with high complication rates such as stent obstruction, stent migration, and airway perforation.[1] Our patient's symptoms improved after initiating CPAP therapy. Therefore, we chose not to proceed with stents or surgical intervention, as we considered the risks to outweigh the benefits.

In conclusion, physicians should be aware of the possibility of TBM as a potential diagnosis in patients who have undergone allogenic HSCT with respiratory complications especially in patients whom spirometer shows abnormal biphasic pattern in flow-volume loop. This knowledge can aid in avoiding misdiagnosis and ensuring appropriate management of this condition.

## AUTHOR CONTRIBUTIONS

Pitirat Panpruang and Dararat Eksombatchai drafted the manuscript. Viboon Boonsarngsuk revised the manuscript; supervision. All authors have read and approved the final version of the manuscript.

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## CONFLICT OF INTEREST STATEMENT

None declared.

## DATA AVAILABILITY STATEMENT

Data available on request from the authors.

## ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

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