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Pulmonary Barotrauma Following Nasal High-Flow Therapy in a Patient with Bronchiolitis Obliterans Syndrome

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Female, 41
Final Diagnosis: Pulmonary barotrauma
Symptoms: Dyspnea
Medication: —
Clinical Procedure: High-flow nasal cannula
Specialty: Pulmonology

Objective: Unusual or unexpected effect of treatment

Background: Pulmonary barotrauma is considered as complication of the use of positive-pressure ventilations. Nasal high-flow therapy is increasingly being used as an alternative to them. Nasal high-flow therapy rarely causes pulmonary barotrauma probably because airway pressures are lower when compared with invasive mechanical ventilation. Bronchiolitis obliterans syndrome after allogenic hematopoietic stem cell transplantation is triggered by an alloimmune response in the bronchioles and causes obstruction of the bronchioles. However, the threshold of additional positive pressure has not been determined in a patient with bronchiolitis obliterans syndrome.

Case Report: A 14-year-old female patient with acute myeloid leukemia at high risk of recurrence received an allogeneic hematopoietic stem cell transplantation from an unrelated bone marrow donor. After engraftment, she developed acute graft-versus-host disease, followed by chronic graft-versus-host disease. Ten months post-transplantation, she developed bronchiolitis obliterans syndrome. She continued to receive nasal supplemental oxygen therapy for persistent dyspnea due to bronchiolitis obliterans syndrome. At month +25, hypercapnia was noted. Therefore, we carefully initiated nasal high-flow therapy for dyspnea and adjusted the oxygen dose to maintain 90% SpO2 to avoid life-threatening apnea. The flow rate was as low as 14 to 20 L/min to avoid the risk of barotrauma and the deterioration of air trapping. Unfortunately, she died of respiratory failure at month +31 post-transplantation. A lung autopsy revealed pulmonary barotrauma.

Conclusions: Nasal high-flow therapy, even at low flow rates, may cause fatal pulmonary barotrauma in bronchiolitis obliterans syndrome.

MeSH Keywords: Barotrauma • Bronchiolitis Obliterans • Graft *vs.* Host Disease • Noninvasive Ventilation

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Background

Pulmonary barotrauma can be complicated in mechanical ventilation and refers to alveolar rupture due to elevated transalveolar pressure, resulting in conditions including pneumothorax, pneumomediastinum, pneumoperitoneum, and subcutaneous emphysema. Pulmonary barotrauma may be associated with increased mortality and in some circumstances it may be life-threatening. Generally, barotrauma related to positive-pressure ventilation tend to be much less common during non-invasive ventilation, such as nasal high-flow therapy (NHFT), than invasive positive-pressure ventilation. We experienced a case of fatal barotrauma following NHFT with flow rate as low as 14 to 20 L/min during treatment for bronchiolitis obliterans syndrome (BOS) in the state of chronic graft-*vs.*-host disease (GVHD). We have discussed pathophysiology of barotrauma related to NHFT in BOS.

Case Report

A 14-year-old female patient developed high-risk acute myeloid leukemia with MLL-AF6 fusion gene. Allogeneic hematopoietic cell transplantation was performed during complete remission from an allele HLA 6/6-matched, unrelated bone marrow donor. Myeloablative regimen consisted of busulfan and melphalan. After engraftment on day 21, she developed grade III acute graft-versus-host disease (GVHD), involving skin, liver, and gut. She had been treated with methylprednisolone, oral beclomethasone dipropionate, and mycophenolate mofetil, followed by mesenchymal stromal cell therapy for steroid-refractory acute GVHD, resulting in stable state. Then, she developed extended chronic GVHD involving skin, liver, eye, and buccal mucosa. Subsequently, she was placed on prednisolone, tacrolimus, and mycophenolate mofetil. Ten months post-transplantation, she developed exertional dyspnea with crackles (Figure 1A). There were no data suggesting infections. High-resolution chest computed tomography (CT) scan revealed pulmonary hyperinflation with mild pneumomediastinum, and small airway thickening with bronchiectasis (Figure 1B), suggesting bronchiolitis obliterans syndrome (BOS) [1]. Parametric response mapping testing was not available [2]. BOS signs and symptoms included dyspnea during exertion, reduced exercise tolerance, wheezing, and pneumomediastinum. We could not perform a respiratory function test because of swollen, painful lip mucosa due to chronic GVHD. Furthermore, the examination itself might have some risk of worsening the pneumomediastinum. We were reluctant to perform a lung biopsy because of possible high morbidity in this patient. At month +11 post-transplantation, nasal supplemental oxygen therapy was instituted for pneumomediastinum with BOS, followed by FAM therapy (inhalation of fluticasone, azithromycin, and montelukast) with systemic glucocorticoid. FAM therapy with systemic glucocorticoid may avoid progression of new-onset BOS [3]. Long-term systemic glucocorticoid and drugs that harm lymphocyte proliferation and activation (such as calcineurin inhibitors) have formed the mainstay of BOS therapy. While the patient's pneumomediastinum was improving, she continued to receive nasal supplemental oxygen therapy for persistent dyspnea. At month +25, she had persistent nonproductive cough. Fever, elevated serum C-reactive protein, weight loss, malaise, and worsened dyspnea appeared during the next 2 weeks. At this point, hypercapnia was noted (PvCO2: 100 mm Hg). Repeated chest CT revealed migratory pulmonary opacities. She was clinically diagnosed as having cryptogenic organizing pneumonia (COP). Prednisolone was increased from 0.5 mg/kg/day to 2 mg/day at month +26. Then, the pulmonary opacities disappeared, and her hypercapnia improved, but dyspnea persisted. We carefully initiated NHFT for dyspnea and adjusted the oxygen dose to maintain 90% SpO2 to avoid life-threatening apnea. The flow rate was as low as 14 to 20 L/min to avoid the risk of barotrauma and the deterioration of air trapping. Unfortunately, respiratory status worsened despite methylprednisolone pulsed therapy and she died at month +31 post-transplantation. A partial lung autopsy revealed that there was alveolar overdistension and destruction of alveolar septa without inflammatory fibrotic occlusion of the small airways, in other words, no evidence of bronchiolitis obliterans or COP in this autopsied sample (Figure 1C). These findings were compatible with the diagnosis of pulmonary barotrauma.

Discussion

BOS consisted of fibrotic occlusion followed by obstruction of bronchioles. BOS is often an insidious disease and develops within 2 years of transplantation. The diagnosis depends on obstructive reduction of pulmonary function in the absence of other etiologies [4]. The 3-year survival rate from the time of transplantation to diagnosis of BOS was 29.9% (284–466 days), and 16.8% (< 284 days) [5]. Because BOS patients have significant air trapping with fixed small airway obstruction, which increases the risk of barotrauma and worsens air trapping, additional positive pressure should be minimized [4]. Unfortunately, the optimal level of positive pressure has not yet been determined. Since our patient preferred heated, and humidified gas and nasal supplemental oxygen therapy appeared not to be effective, we carefully instituted NHFT for progressive dyspnea and adjusted the oxygen dose to 90% SpO2 to avoid life-threatening apnea. However, SpO2 progressively decreased following NHFT (Figure 1A). Before an autopsy was done, we had considered the fatal respiratory failure was mainly due to BOS. A percutaneous lung autopsy from the right ventral chest revealed that there was alveolar overdistension with destruction of alveolar septa, without any indication of

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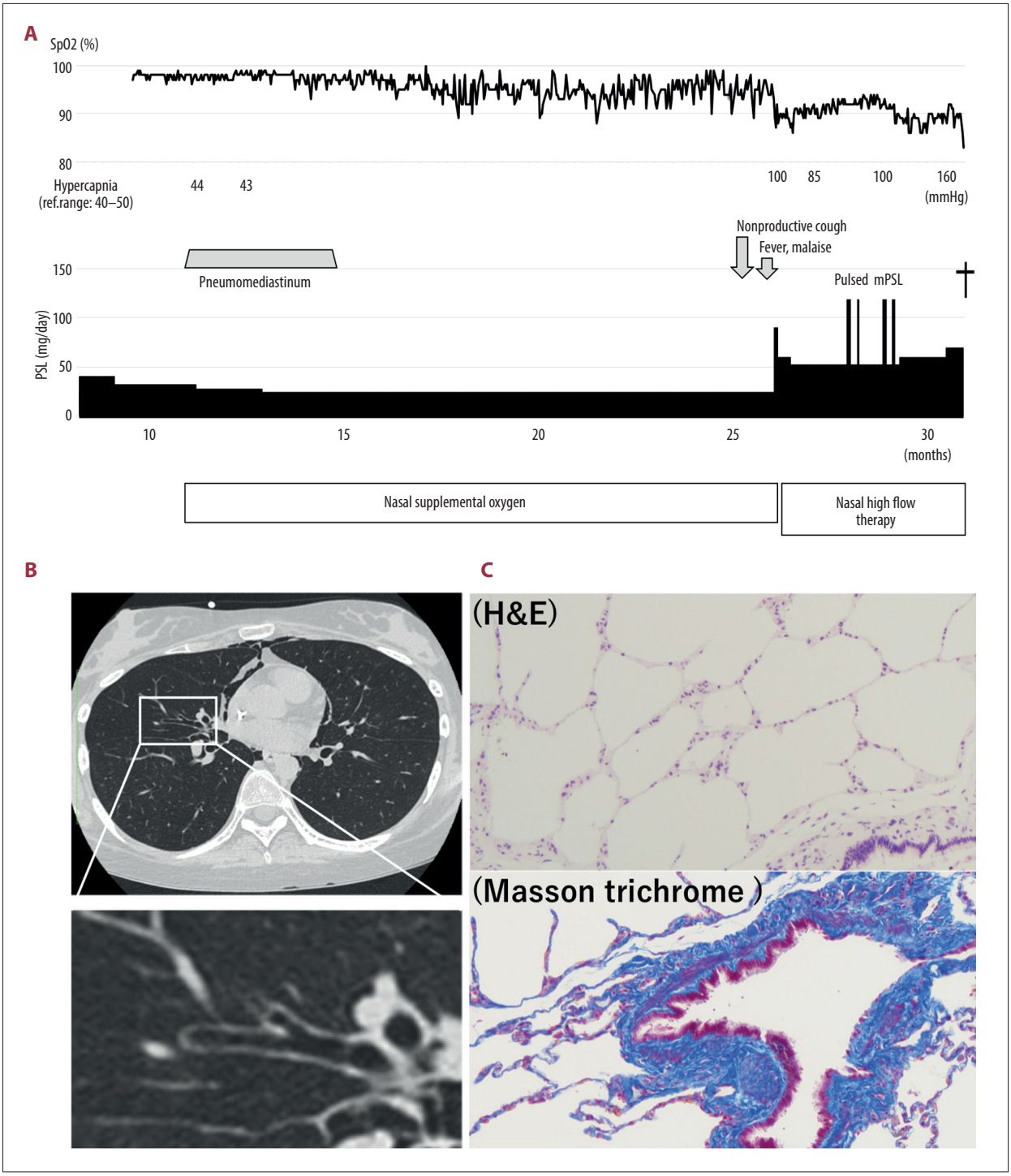

Figure 1. Fatal pulmonary barotrauma related to nasal high-flow therapy. (**A**) Clinical course of barotrauma in the setting of chronic graft-versus-host disease. SpO2 level gradually declined during nasal supplemental oxygen therapy and nasal high-flow therapy. (**B**) High-resolution chest computed tomography scan showed pulmonary hyperinflation with mild pneumomediastinum, and small airway thickening with bronchiectasis, suggesting symptomatic bronchiolitis obliterans syndrome. (**C**) Autopsied pulmonary specimen showed alveolar overdistension with destruction of alveolar septa, indicating pulmonary barotrauma (H&E staining). Mild fibrotic changes and smooth muscle hyperplasia without stenosis or occlusion in bronchioles are evident by Masson trichrome stain. No accumulation of CD3+T cells and CD68+macrophages were observed in immunohistochemical staining (data not shown). PSL – prednisolone; mPSL – methylprednisolone; H&E – hematoxylin and eosin).

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bronchiolitis obliterans or COP (Figure 1C). Collectively, pathological findings suggested that her cause of death was not BOS itself, but pulmonary barotrauma related to NHFT.

NHFT with a simple interface is an increasingly popular for respiratory support in neonates, older children, and adults, although Mayfield et al. reported that there is no evidence for the safety or efficacy of NHFT as a form of respiratory support in children [6]. The mean nasopharyngeal pressure during high-flow oxygen in the nose increases as flow increases. With the mouth closed, the mean airway pressures at 30, 40, and 50 L/min were 1.93, 2.58, and 3.31cm H_2O, respectively [7]. Hegde et al. reported that an otherwise healthy 16-year-old male patient with cerebral palsy who developed pneumomediastinum when he was receiving 20 L/min heated, humidified NHFT and the patient died due to NHFT complications [8]. Why was it that our patient developed a fatal pulmonary barotrauma despite NHFT with flow rate as low as 14 to 20 L/min? First, she already had mild emphysema and pneumomediastinum due to BOS. Second, she may have had chronic lung damage due to long-term oxygen therapy. Oxygen plays a vital role in ATP synthesis; on the other hand, it is responsible for the production of reactive oxygen species, which are capable of damaging alveolar epithelial cells, thus causing disturbances in the pulmonary system and gas exchange impairment [9]. How could our patient have been better treated? Patients at risk for barotrauma may benefit from repositioning, including prone position during NHFT. Guerin et al. showed that patients with acute respiratory distress syndrome (ARDS) and severe hypoxemia can benefit from prone treatment when it is used early and in relatively long sessions [10]. It has been reported that the changes in lung parenchyma after ARDS are significantly more frequent and more pronounced in the ventral than in the dorsal portions of the lung, that is, the dorsal lung may be protected from barotrauma by collapse [11]. There were limitations in this report. The autopsy site was only a ventral portion of the left lung because of sampling restrictions. It is unclear whether other parts of the lung, eg the dorsal portion, had similar pathological findings. A plausible explanation included that FAM therapy was effective enough to revert BOS lung tissue to almost normal, except mild fibrotic changes and smooth muscle hyperplasia in bronchioles [12].

Conclusions

Not only BOS, but chronic lung damage due to long-term oxygenation may be risk factors of fatal lung injury after NHFT, even at low flow rates.

Conflict of interest

None.

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