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【 CASE REPORT 】

Early-onset, Severe Chronic Obstructive Pulmonary Disease with Pulmonary Hypertension that was Likely Induced by Toluene Exposure

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Abstract:
Early-onset pulmonary emphysema is uncommon and its pathogenesis is poorly defined. A 30-year-old man was admitted to our intensive care unit with severe respiratory failure. Besides smoking heavily since the 14 years of age, he had habitually inhaled organic solvents, such as toluene, in his adolescence. High-resolution computed tomography showed evident pulmonary emphysema throughout the lung fields. Based on the findings of right heart catheterization, he was diagnosed with an acute exacerbation of chronic obstructive pulmonary disease complicated with pulmonary hypertension. Heavy smoking from a young age and exposure to toluene were the suspected causes of the patient's severe pulmonary emphysema.

Key words: pulmonary disease, chronic obstructive, severe early-onset, pulmonary hypertension, right-sided heart failure, toluene

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Introduction

Pulmonary emphysema, a type of chronic obstructive pulmonary disease (COPD), is most commonly seen in patients over 60 years of age who smoke (1). Early-onset pulmonary emphysema is defined as a disease onset before the 55 years of age with or without a smoking history (2). Because the latter is a rare condition, its pathogenesis and risk factors are unclear. We present the case of a 30-year-old man who developed early-onset and severe pulmonary emphysema. Because his pulmonary function was so severely impaired, he also developed secondary pulmonary hypertension. The patient had a history of smoking from a young age and had habitually inhaled paint thinners such as toluene, which might have been related to the early onset of his COPD.

Case Report

A 30-year-old man was admitted to our hospital with fever and severe dyspnea of modified medical research council (mMRC) dyspnea grade 4. He had experienced dyspnea on exertion since 27 years of age, and had barely been able to walk for the previous 6 months. Following the development of fever and cough 3 days prior to admission, his symptoms worsened daily; on arrival he could barely speak. His medical history included nephrotic syndrome and asthmatic bronchitis in childhood. He had also been diagnosed with COPD at 29 years of age, but was only treated with short-acting salbutamol sulfate as needed because of his poor compliance. He had smoked 40 cigarettes daily since 14 years of age and had continued smoking until admission. In addition to smoking, he reported that he had habitually inhaled paint thinners and other organic compounds on daily basis (throughout the day) for approximately one and a half years from 18 years of age.

On examination, he was malnourished; he weighed only 39 kg and his body mass index of 16.8 kg/m^2. His vital signs were as follows: body temperature, 38.2℃; heart rate, 138 beats/min (tachycardia), and respiratory rate, 35 breaths/

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Table 1. Laboratory Data on Admission.

Hematology		Biochemistry		Serology	
WBC	5,050 /μL	Alb	3.0 g/dL	CRP	9.83 mg/dL
Neu	72.3 %	T-Bil	0.7 mg/dL	BNP	143.5 pg/mL
Lymph	16.5 %	AST	375 IU/L		
Eosino	0.2 %	ALT	311 IU/L	Arterial blood gas analysis	
RBC	4.96×10^4 /μL	LDH	413 IU/L	(PEEP 3cmH_2O FiO_2 0.78)	
Hb	16.0 g/dL	CK	155 IU/L	pH	7.33
Ht	44.4 %	BUN	23.4 mg/dL	pCO_2	56 mmHg
Plt	13.4×10^3 /μL	Cre	0.83 mg/dL	pO_2	401 mmHg
		Na	141 mmol/L	HCO_3	29.5 mmol/L
Coagulation		K	4.8 mmol/L	Lac	2.0 mmol/L
PT-INR	1.49				
APTT	44.3 sec				
Fibrinogen	322.2 mg/dL				
D-dimer	1.7 μg/mL				

WBC: white blood cell, Neu: neutrophil, Lymph: lymphocyte, Eosino: eosinophil, Hb: hemoglobin, Ht: hematocrit, Plt: platelet, Alb: albumin, T-Bil: total bilirubin, AST: aspartate transaminase, ALT: alanine transaminase, LDH: lactate dehydrogenase, CK: creatinine phosphokinase, Cre: creatinine, Na: sodium, K: potassium, CRP: C-reactive protein, BNP: brain natriuretic peptide, PT-INR prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, FDP: fibrin degradation products, PEEP: positive end expiratory pressure, Lac: lactate

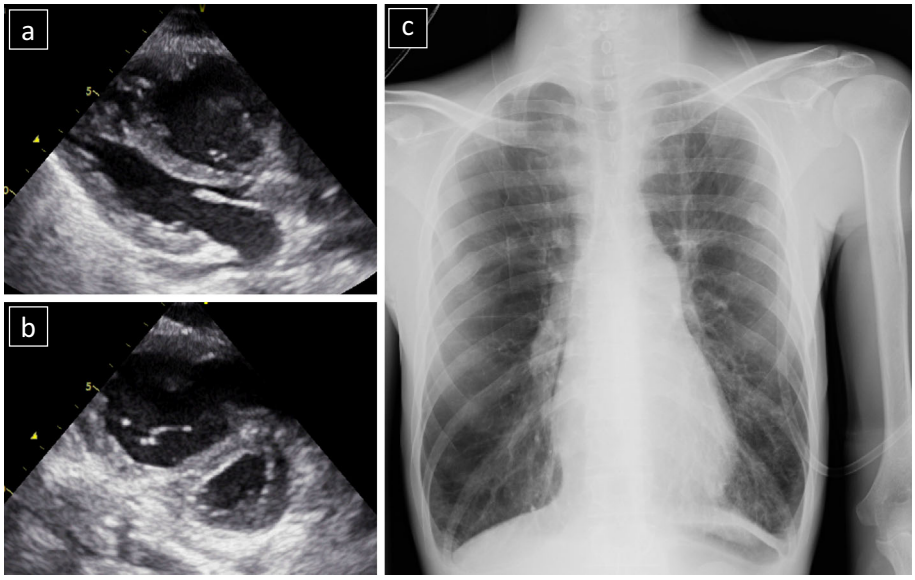

Figure 1 a: Echocardiography showing a D-shaped right ventricle. b: The right ventricle is dilated, compressing the left atrium and ventricle. c: A chest radiograph obtained on admission. Hyper-inflated lung fields are apparent.

min (tachypnea). Oximetry revealed that his oxygen saturation was 95% on 10 L/min oxygen with a reservoir-type mask. His respiratory sounds had almost disappeared, leaving slight wheezing bilaterally. Cardiac auscultation revealed no abnormalities. Leg edema and skin lesions were not observed. Blood tests showed normal blood counts, but elevated levels of C-reactive protein, hepatic enzymes, and brain natriuretic peptide (BNP), indicating a viral infection and congestive hepatopathy (Table 1). Blood tests also revealed that he was negative for hepatitis B (HBV) and human immunodeficiency virus (HIV), but positive for hepatitis C (HCV). He was not tested for human T-lymphotropic virus type (HTLV)-1. On echocardiography, the cardiac ejection fraction was 68.2% with an E/E' value of 6.15, indicating a normal left cardiac function, but the right ventricle was dilated with a flattened interventricular septum (Fig. 1). An anterior-posterior chest radiograph revealed hyperinflated bilateral lung fields with a low-lying diaphragm and teardrop heart (Fig. 1).

He was treated with short acting bronchodilators and intravenous hydrocortisone and theophylline based on the initial suspicion of a bronchial asthma attack. However, his

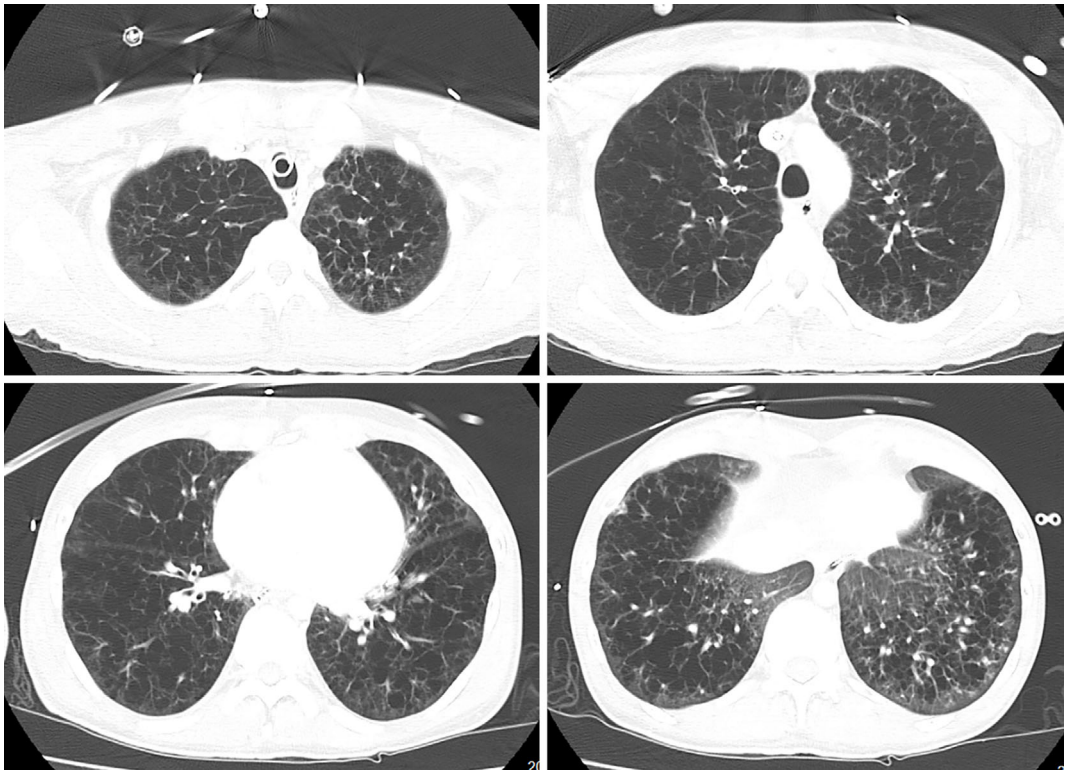

Figure 2. High-resolution computed tomography (HRCT) of the thorax. Diffuse low attenuation areas and bullas are seen throughout the lung fields.

tachycardia and tachypnea showed no improvement despite the initial treatments. He was therefore intubated and mechanical ventilation was initiate. An arterial blood gas that was performed immediately after intubation showed the following results: partial pressure of carbon dioxide in arterial blood ($PaCO_2$) (56 Torr) and partial pressure of arterial oxygen (PaO_2) (401 Torr) with fraction of inspiratory oxygen (FiO_2) (0.78 [P/F ratio 514]) under synchronized intermittent mandatory ventilation (SIMV) in volume-controlled mode with a tidal volume of 330 mL, a respiratory rate of 16/min and a positive end-expiratory pressure (PEEP) of 3 cm H_2O (Table 1).

Thoracic high-resolution computed tomography, which was performed after intubation, revealed diffuse areas of low attenuation and bullas throughout the lung fields; normal lung fields were only retained at the very bottom of the lower lobes (Fig. 2). There was no apparent pneumonia, but bronchial wall thickening was observed in comparison to a CT scan performed at another hospital 8 months prior to admission, suggesting acute bronchitis. There was no apparent pulmonary thrombosis or deep vein thrombosis above knee level that required treatment. *Haemophilus influenzae* was detected in the patient's sputum. The patient's urine was negative for antigens for *Streptococcus pneumoniae* and *Legionella pneumophilia*. Based on his history of heavy smoking and the CT findings, we diagnosed the patient with an acute exacerbation of COPD induced by bronchitis, complicated with right heart failure.

The patient was treated for COPD and right heart failure in our intensive care unit (Fig. 3). Vasoconstrictor support was provided during treatment. However, his arterial CO_2 accumulation and congestion worsened. The placement of a Swan-Ganz catheter on the 5th day after admission revealed a mean pulmonary artery pressure of 35 mmHg, suggesting right heat failure with pulmonary hypertension. His cardiac index was 3.4 L/min/m^2 and it remained within the normal range throughout the monitoring period. The analysis of the patient's hemodynamic variables allowed us to adjust the doses of inotropic agents and diuretics, which improved the pulmonary arterial pressure. The patient's respiratory failure also improved and he was extubated on the 11th day after admission. He was able to leave the intensive care unit on the 14th day after admission. However, he still required non-invasive positive pressure ventilation due to hypercapnia ($PaCO_2$, 53.1 Torr).

Once stabilized, on the 16th day after admission he underwent spirometry (SUPER SPIRO D-21 FXII, CHEST, Japan) which suggested severe airflow obstruction, an excessive residual volume, and an impaired diffusion capacity (Table 2 and Fig. 4). Follow-up right heart catheterization on the 26th day after admission showed a mean pulmonary arterial pressure of 28 mmHg, which still met the criteria for pulmonary hypertension. On the 32nd day after admission, he was discharged from our hospital with medication, home oxygenation therapy and 24-hour non-invasive positive pressure ventilation (for as long as possible) due to severe type 2 respiratory failure and secondary pulmonary hypertension. Nephelometry (SRL, Tokyo, Japan) subsequently revealed that his serum alpha-1 anti-trypsin level, which was examined on the 4th day after admission, was 222 mg/dL (nor-

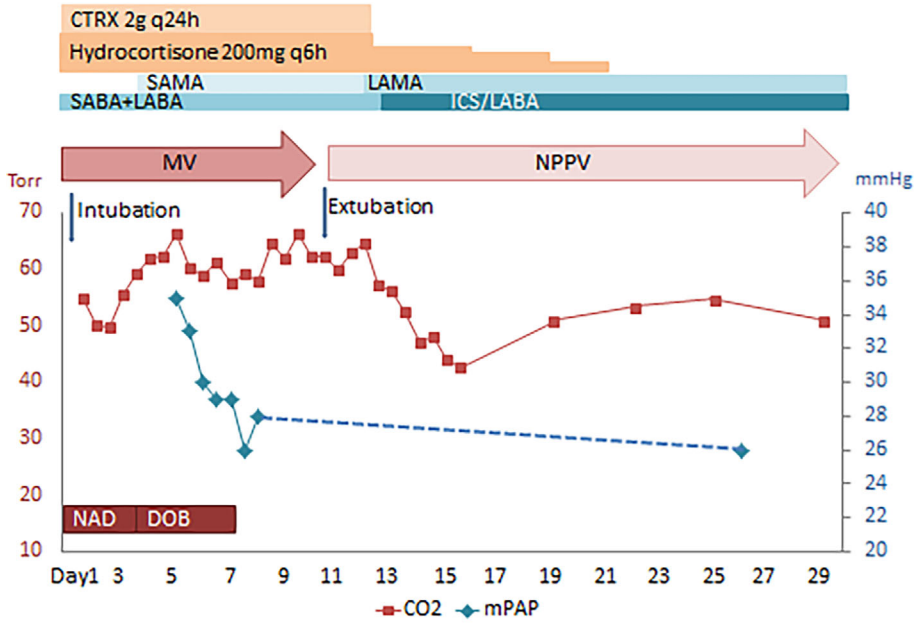

Figure 3. **The patient was treated with hydrocortisone, theophylline, and repeated short acting beta stimulant inhalation and long acting beta stimulant attachment, along with antibiotic therapy with ceftriaxone sodium hydrate. A Swan-Ganz catheter was placed on the 5th day after admission to monitor the patient's hemodynamics. The mean pulmonary arterial pressures and arterial CO_2 levels are shown. The pulmonary arterial pressure decreased following the adjustment of the doses of catecholamine and diuretic agents, and the patient was extubated on the 11th day after admission. The corticosteroid dosage was tapered after extubation. CTRX: Ceftriaxone, SAMA: short acting muscarinic antagonist, LAMA: long acting muscarinic antagonist, SABA: short acting beta-2 agonist, LABA: long acting beta-2 agonist, ICS: inhaled corticosteroids, MV: mechanical ventilation, NPPV: non-invasive positive pressure ventilation, NAD: noradrenaline, DOB: dobutamine, mPAP: mean pulmonary artery pressure**

Table 2. **The Results of Spirometry Before Discharge.**

FVC	2.14 L
%FVC	53.6 %
$FEV_{1.0}$	0.64 L
$FEV_{1.0}$%	29.9 %
%$FEV_{1.0}$	34.0 %
FRC	4.27 L
RV	3.15 L
RV/TLC	58.4 %
DLCO	3.13 mL/min/mmHg
%DLCO	16 %
DLCO/VA	0.74 mL/min/mmHg/L

FVC: forced vital capacity, FEV1.0 forced expiratory volume in 1 second, FRC: functional residual capacity, RV: residual volume, TLC: total lung capacity, DLCO: diffusing capacity, VA: alveolar volume

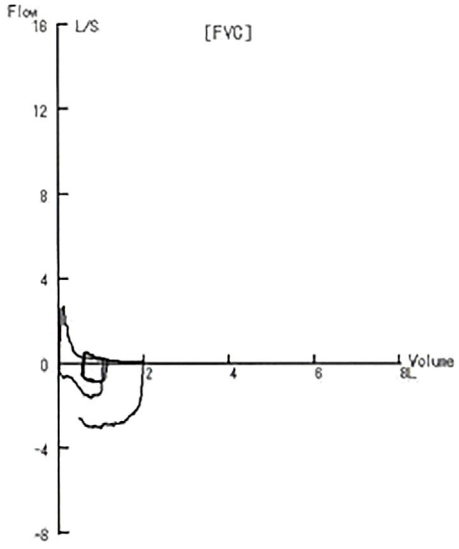

Figure 4. **The spirometry findings.**

mal range 94-150 mg/dL). He had no noteworthy family history or any hereditary disorders.

We hypothesized that the elevation in hepatic enzymes was due to congestive liver disease, although the patient was positive for HCV and his HCV-RNA level was 6.2 log. On echography, the hepatic veins and inferior vena cava were dilated, suggesting congestion. In addition, morphological changes and abdominal lymphadenopathy were not observed, and there no finding that were suggestive of chronic or acute hepatitis. The fact that the patient's transaminase levels gradually declined and normalized on the 25th day after admission without any treatment (other than the above-

mentioned treatments) supports this hypothesis. However, the presence of liver fibrosis should be investigated since viral infection might have contributed to this abnormality and delayed its improvement.

It is not clear whether the patient had asthma, due to his young age and history of childhood asthma. His sputum, which was tested on the 4th day after admission, was negative for eosinophils, but since it was taken after the administration of steroids, the result might have a been false negative. However, the patient had no food or drug allergies, allergic rhinitis, or atopic dermatitis. In addition, when he underwent further testing at more than 6 months after discharge, his eosinophil counts were normal and total immunoglobulin E (IgE) and specific IgE (associated with asthma) by radioimmunosorbent testing (RIST) were negative. The absence of any asthmatic features made it difficult to diagnose him with asthma COPD overlap syndrome (ACOS).

Discussion

We experienced a case of early-onset and severe pulmonary emphysema with pulmonary hypertension. A number of factors may lead to the pathogenesis of emphysema, but the main inducer in this patient is suspected to have been the habitual inhalation of toxic organic compounds during adolescence.

Pulmonary emphysema usually occurs at 60 to 80 years of age, and is defined as being early-onset when the disease develops before 55 years of age (1). Not surprisingly, early-onset pulmonary emphysema is a rare condition. In Japan, there are fewer than 100 patients with a Fletcher-Hugh-Jones (FHJ) class of II or more, and an $FEV_{1.0}$ of <50% of the predicted value (2). The most significant risk factor for pulmonary emphysema is cigarette smoking, and alpha-1 antitrypsin deficiency has been established as a risk factor for early-onset pulmonary emphysema, which is said to present with emphysema in the fourth to fifth decades of life (1, 3). Other genetic and environmental factors such as Marfan syndrome, Ehlers-Danlos syndrome, intravenous drug abuse, exposure to deleterious gases, and HIV infection, may contribute to the development of emphysema, but the details remain unclear (4, 5).

The present patient was diagnosed with pulmonary emphysema without alpha-1 antitrypsin deficiency at 30 years of age, which is considerably younger than the usual cut-off for early-onset pulmonary emphysema. Active smoking from 14 years of age is an evident risk factor. It is also known that active or passive exposure to cigarette smoke at a young age can cause a 5-10% deterioration in an individual's $FEV_{1.0}$ value by 20 years of age, indicating that the patient's passive smoking as a young child due to his parents' smoking habits might have also been related to the onset of disease (6). Nonetheless, it remains uncertain whether cigarette smoke alone was responsible for the very severe COPD of Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification of 4 (1).

Besides smoking, he had a history of habitually inhaling of paint thinners, which may also be a risk factor for pulmonary emphysema. Many organic compounds, commonly toluene and benzene, are used as solvents to thin oil-based paints (7). Exposure to vapors from these compounds is considered hazardous, and is associated with the development of occupational asthma and COPD symptoms (8). A study of workers in a toluene-related compound industry showed a significant decline in the $FEV_{1.0}$ values of subjects who had higher exposure to toluene, indicating that the detrimental effects of toluene are related to the development of COPD (9). It is now known that exposure to toluene and benzene together result in cell death with irreversible DNA damage in alveolar cells (7). It has been suggested that this alveolar damage may lead to the development of emphysema. Tsuchida et al. reported a case of early-onset pulmonary emphysema in a patient who was 27 years of age. The patient had started smoking at 14 years of age and also had a history of occupational exposure to organic solvents (for a number of years) (10). These findings suggest that along with smoking from an early age, the inhalation of toluene may induce early-onset pulmonary emphysema in patients with a normal alpha-1-antitrypsin level.

The detailed mechanism underlying the development of pulmonary emphysema in individuals who are exposed to toluene is unknown. In addition, it remains unclear why smoking and exposure to organic compounds causes some patients to develop COPD at a very young age. Kelleher et al. reported a genetic variant in patients with early-onset COPD, suggesting that a genetic factor other than alpha-1 antitrypsin deficiency affects the susceptibility to emphysema (11). Further studies will be necessary to elucidate the pathogenesis of early onset pulmonary emphysema.

We examined the patient's alpha-1 antitrypsin level on the 4th day after admission and found it to be above the normal range, suggesting that he did not have alpha-1 antitrypsin deficiency. Alpha-1 antitrypsin is an acute phase protein that is produced by liver in response to various stimuli including inflammatory mediators (12). Silverman et al. reported that patients who are heterozygous for alpha-1 antitrypsin deficiency have alpha-1 antitrypsin levels that are within (or near) the normal range, and that the alpha-1 antitrypsin level may increase during inflammatory stress (13). Since we did not reexamine the alpha-1 antitrypsin level of this patient, it is hard to deny the possibility that this patient was heterozygous for alpha-1 antitrypsin deficiency. Nevertheless, it is also known that the level of alpha-1 antitrypsin is significantly reduced in nephrotic patients due to urinary excretion (14). A history of nephrotic syndrome may have been related to the pathogenesis in the present case. Although the details were unknown, since his medical records had already been discarded, the patient's parents reported that, he had been frequently admitted to hospital for nephrotic syndrome for most of his elementary school life and had been treated with corticosteroids. It is suspected that his alpha-1 antitryp-

sin level had been below normal for a certain period. Even though the patient did not have alpha-1 antitrypsin deficiency, this medical history and steroid therapy may have resulted in his rapid deterioration due to exposure to toxic substances and to his susceptibility to these effects.

Our patient developed pulmonary hypertension in addition to early-onset pulmonary emphysema. It is well known that pulmonary hypertension is associated with pulmonary diseases that cause hypoxemia such as COPD (15). Because right heart catheterization is necessary for its diagnosis, the true prevalence of pulmonary hypertension in COPD is unknown. Thabut et al. reported that 50.2% of patients with severe COPD had pulmonary hypertension in their study of 215 patients who candidates for lung volume reduction or lung transplantation. The patients showed relatively moderate pulmonary hypertension with a mean pulmonary artery pressure of 26.9 mmHg (16). Our patient also had moderate pulmonary hypertension; thus, our findings are consistent with their study. Echography at 2 years after hospital admission showed that the estimated right ventricle pressure was 32 mmHg, indicating improvement. At the same time, residual right ventricle overload was observed, even after overcoming the exacerbation. The pathophysiology of secondary pulmonary hypertension is considered multifactorial. It includes factors such as alveolar hypoxia, the loss of the pulmonary vascular bed following lung parenchyma destruction, inflammation, and a genetic predisposition-all of which may result in hemodynamic alteration (15). In our case, pulmonary hypertension complicated the patient's severe respiratory failure, and will have a profound impact on both his functional capacity and survival.

In conclusion, we herein reported a case of early-onset and severe pulmonary emphysema induced by toluene exposure. Although the patient was only 30 years of age, his COPD was so severe that it coexisted with pulmonary hypertension. The patient requires continuous follow-up, and a lung transplant will be considered for his long-term survival.

The authors state that they have no Conflict of Interest (COI).

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