

[ CASE REPORT ]

## Bloody Bronchial Cast Formation Due to Alveolar Hemorrhage Associated with H1N1 Influenza Infection

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### Abstract:

A previously healthy 55-year-old man with H1N1 influenza A presented with severe respiratory failure and cardiac arrest. Following the return of spontaneous circulation, venovenous extracorporeal membrane oxygenation was required to maintain oxygenation. On day 2, bronchoscopy revealed a bloody bronchial cast obstructing the right main bronchus. A pathological examination revealed that it was composed of intrabronchial and intra-alveolar hemorrhagic tissue. Unfortunately, the patient died due to severe brain ischemia; a subsequent autopsy revealed marked alveolar hemorrhage. It is possible that anticoagulant therapy, alveolar collapse, and neuromuscular blocking agents provoked cast development in this case.

**Key words:** ECMO, complication, anticoagulation, plastic bronchitis, white out, alveolar collapse

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### Introduction

H1N1 influenza A infection is associated with severe respiratory failure and high mortality rates (1). In children, such an infection sometimes results in bronchial cast development, which can obstruct the main bronchi and lead to a potentially life-threatening condition known as plastic bronchitis (2). However, bronchial casts have not been reported in association with this infection in adults.

### Case Report

A previously healthy 55-year-old man complaining of fever and dyspnea collapsed a few minutes before arriving at our emergency department. Upon arrival, the patient was in cardiac arrest, and spontaneous circulation returned after 10 minutes of resuscitation. An arterial blood gas assessment on admission revealed metabolic and respiratory acidosis; the laboratory data showed no apparent cause of cardiac arrest (Table). Chest computed tomography (CT) indicated bilateral patchy infiltration (Fig. 1-A).

While intubated and under positive pressure ventilation, bloody bubbles-indicative of alveolar hemorrhage-were

noted in the tracheal tube. Moreover, the patient's percutaneous oxygen saturation (SpO<sub>2</sub>) level was persistently below 80-90% despite an FiO<sub>2</sub> (fraction of inspired oxygen) of 1.0 and a mean airway pressure > 30 cm H<sub>2</sub>O. Based on these persistent findings, we initiated venovenous extracorporeal membrane oxygenation (VV-ECMO) in the intensive care unit at 4 hours after admission. The ventilator was set at "lung rest." The initiation of VV-ECMO stabilized the patient's respiratory condition. Due to the cardiac arrest, we also induced hypothermic temperature management at 35°C. The results of a rapid antigen influenza test were negative; however, a polymerase chain reaction of the patient's respiratory secretions, which were obtained by bronchoscopy, revealed H1N1 influenza A virus. Moreover, bacterial cultures of the sputum, bronchoscope, and blood on admission revealed no other bacterial infections. Based on these findings, we diagnosed the patient with an H1N1 influenza A infection and provided empiric treatment with the antiviral agent peramivir (600 mg/day) and the antibiotic meropenem (3 g/day).

On day 1, chest radiography revealed severe consolidation of both lungs (Fig. 1-B), which was consistent with the phenomenon known as "whiteout," which is characterized by diffuse alveolar collapse due to decreased airway pressure.

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**Table 1. Laboratory Test and Atrial Blood Gas Assessment on Admission.**

[CBC]		[Coagulation]	
WBC	18,800/ $\mu$ L	PT-INR	1.23
RBC	398*10 <sup>4</sup> / $\mu$ L	APTT	200> sec
Hb	12.1 g/dL	Fib	560 mg/d
Ht	35.0 %		
Plt	12.5 *10 <sup>4</sup> / $\mu$ L		
[Chemistry]		[Atrial blood gas]	
AST	141 U/L	pH	6.751
ALT	82 U/L	PaCO <sub>2</sub>	85.6 mmHg
CPK	1,929 U/L	PaO <sub>2</sub>	71.9 mmHg
Cr	0.64 mg/d	HCO <sub>3</sub> <sup>-</sup>	11.2 mmol/L
BUN	17.3 mg/d	Base excess	-25.7 mmol/L
Na	142 meq/L	Lac	18.0 mmol/L
K	3.8 meq/L		(FiO <sub>2</sub> 1.0)
Cl	104 meq/L		
CRP	14.0 mg/d		

This occurred because the maintenance of high airway pressure was unnecessary under VV-ECMO. In addition, bronchoscopy on day 1 revealed diffuse alveolar hemorrhage (Fig. 2-A).

On day 2, bronchoscopy revealed the presence of a bloody bronchial cast, which totally obstructed the right main bronchus (Fig. 2-B), and which we were unable to remove. However, we were finally able to remove the cast on day 5 by aggressive bronchoscopic intervention (Fig. 3-A). Macroscopically, the cast extracted from the right bronchus was dark red in color and had retained the shape of the bronchial tree. A microscopic analysis revealed that the cast was mainly composed of red blood cells along with fibrin, neutrophils, and necrotic debris. Mucin was detected focally on the surface of (but not inside) the cast. The cast was defined as a blood clot composed of intrabronchial or intra-alveolar hemorrhagic tissue (Fig. 3-B).

After removing the cast, the patient's respiratory condition dramatically improved, and he was weaned off VV-ECMO on day 6. Although his respiratory condition stabilized, head CT revealed severe cerebral edema from the initial cardiac arrest: at this time, his pupils were dilated with an absent pupillary light reflex. Given that his neurological prognosis was predicted to be severe, his family consented to the withdrawal of intensive treatment, and he died on day 11. His family consented to autopsy.

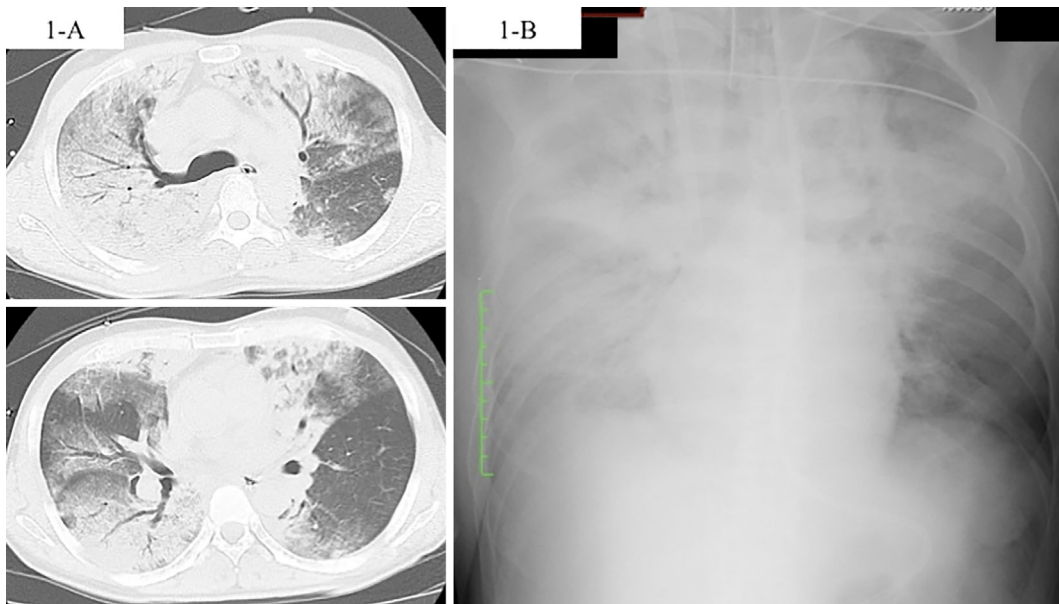
At autopsy, the right and left lungs weighed 863 g and 851 g, respectively. On histological assessment, focal edema, intra-alveolar hemorrhage, fibrinous exudate, and hyaline membrane were noted. Although the intra-alveolar hemorrhage was substantial, no intrabronchial coagulation was detected. In the middle and lower lobes, neutrophilic infiltration was present in and around the bronchioles and in the alveolar spaces, indicating the presence of secondary bacterial bronchopneumonia (Fig. 4).

## Discussion

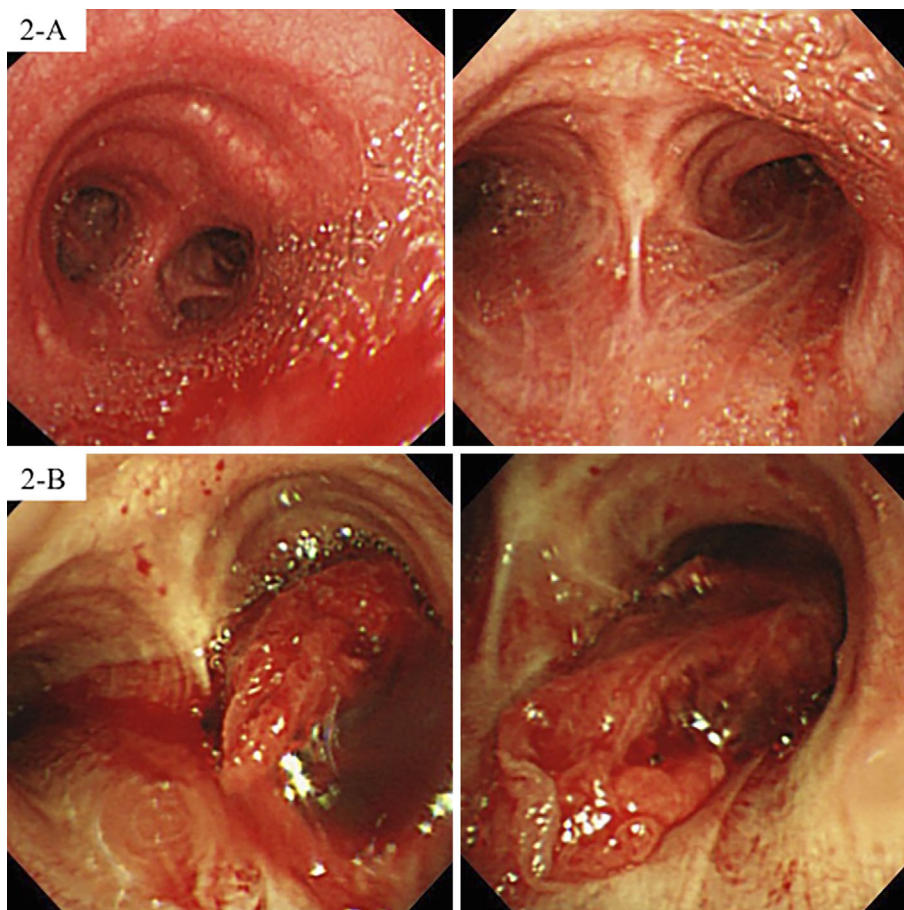
We herein describe a rare case in which a bloody bronchial cast formed due to an alveolar hemorrhage in an adult patient with H1N1 influenza A. Plastic bronchitis, characterized by bronchial cast formation, is a well-known but rare cause of severe respiratory failure in children, and has been associated with H1N1 influenza A (2). Bronchial casts, which are diagnosed by bronchoscopy, are typically white in color and are classified as either inflammatory or acellular types (3). The inflammatory type, which is associated with infection, asthma, and other inflammatory diseases, is composed of fibrin, eosinophils, and neutrophils. The acellular type, which is associated with congenital heart disease, is composed of mucin with little or no cellular infiltration (3). Consistent with these reports, the bloody bronchial cast in our case exhibited features of typical plastic bronchitis, including the production of sudden airway obstruction, the preserved shape of the bronchial tree, and the fact that it was associated with H1N1 influenza A infection. However, because the cast was red and was composed mainly of red blood cells—and because it was pathologically diagnosed as a blood clot, we believe that the pathogenesis was distinct from that associated with typical plastic bronchitis. A few other cases of bloody bronchial casts associated with pulmonary hemorrhage have been reported in coagulopathy disorders, such as Vitamin K deficiency (4-7). Thus, it is possible that our patient's cast had been caused by alveolar hemorrhage and coagulopathy.

Alveolar hemorrhage is a predominant pathological feature of H1N1 influenza infection (8), and an increased incidence of alveolar hemorrhage has been observed in patients with cardiovascular diseases or coagulopathies (9). Although the mechanism remains unclear, research in mice suggests that a tissue factor deficiency in the epithelial cells of the lung may be associated with alveolar hemorrhage in H1N1 influenza (10). Anticoagulation, which is essential in VV-ECMO management, may increase the patient's risk of hemorrhage (11). In our case, severe diffuse alveolar hemorrhage was revealed by bronchoscopy and confirmed by autopsy. It is therefore possible that H1N1 influenza infection and anticoagulation therapy provoked the severe alveolar hemorrhage and promoted the formation of the bloody bronchial cast.

Alveolar collapse may be another factor involved in cast development. Indeed, we did not observe the cast during the bronchoscopy examination at admission—it only appeared on day 2 after the whiteout phenomenon was observed. Whiteout typically presents as complete, dense consolidation on chest X-rays, and is characterized by diffuse alveolar collapse and fluid migration (12). In tandem with this, H1N1 influenza A virus infection in type 2 pneumocytes have been shown to impair surfactant secretion and to affect the maintenance of the alveolar space, which may also lead to alveolar collapse (1). The use of protective lung management (i.



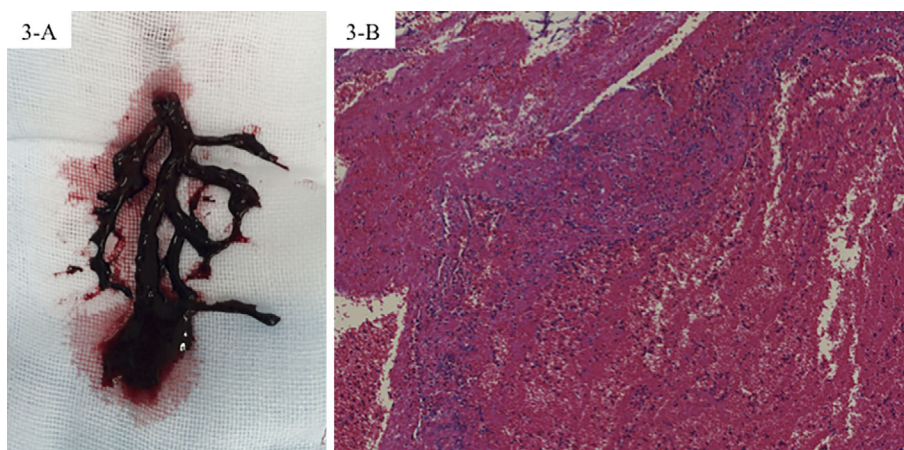
**Figure 1.** A: Bilateral patchy infiltration was observed on chest computed tomography at admission. B: Severe consolidation in both lungs on chest radiography, known as whiteout, after the initiation of venovenous extracorporeal membrane oxygenation.



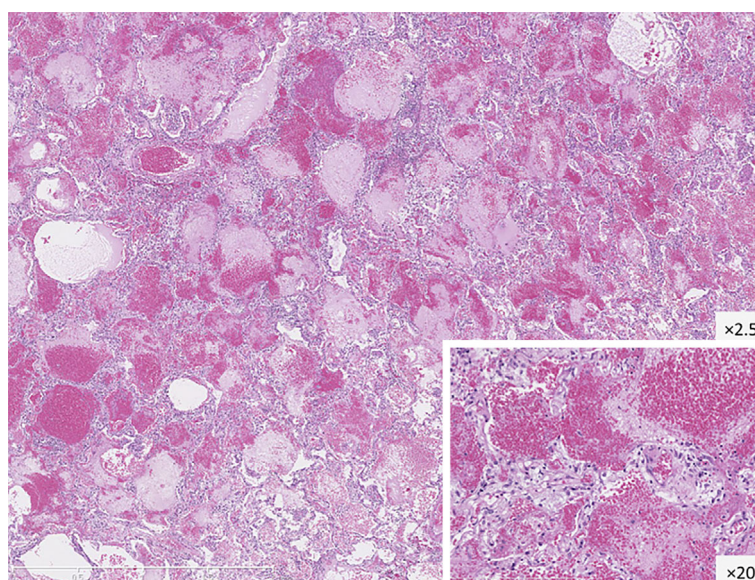
**Figure 2.** A: Bronchoscopy on day 1 showing alveolar hemorrhage without a cast. B: Bronchoscopy on day 2 showing a bloody bronchial cast totally obstructing the right main bronchus.

e., lung rest) further decreases the peak inspiratory airway pressure during VV-ECMO and may further contribute to alveolar collapse (12). In tandem with this process, hyperoxemia and the increased production of reactive oxygen species





**Figure 3.** A: A macroscopic image of the bloody bronchial cast that was removed from the right main bronchus. B: The microscopic pathological findings of the cast extracted from the right bronchus. The extracted cast was mainly composed of red blood cells, together with fibrin, neutrophils, and necrotic debris (Hematoxylin and Eosin staining, 100 $\times$ ).



**Figure 4.** Microscopic pathological findings at autopsy (Left lung, upper lobe). Edema, intra-alveolar hemorrhage, and fibrinous exudation can be seen (Hematoxylin and Eosin staining, 2.5 $\times$ , 20 $\times$ ).

during VV-ECMO can induce platelet activation, aggregation, and thrombosis (12), and may have contributed to bloody cast development in this case. We think that H1N1 influenza A infection coupled with the protective lung management by VV-ECMO might have resulted in alveolar collapse and promoted cast development. Moreover, the use of neuromuscular blocking agents might have contributed further, because these agents suppress the cough reflex, which would have made it difficult to expel the alveolar hemorrhage.

### Conclusions

We described a rare adult case of bloody bronchial cast formation due to alveolar hemorrhage associated with H1N1 influenza A infection. We hypothesize that anticoagulation therapy, alveolar collapse, and neuromuscular blocking

agents provoked cast development. However, due to the lack of reports concerning bloody bronchial casts in association with H1N1 influenza A, some other unknown factors may be involved. The accumulation of further case reports is necessary to elucidate the pathogenesis of bloody cast development in adults with H1N1 influenza A.

Written informed consent for the publication of this case report was obtained from the patient's next-of-kin.

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

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## References

1. Shieh WJ, Blau DM, Denison AM, et al. 2009 pandemic influenza A (H1N1): pathology and pathogenesis of 100 fatal cases in the United States. *Am J Pathol* **177**: 166-175, 2010.
2. Deng J, Zheng Y, Li C, Ma Z, Wang H, Rubin BK. Plastic bronchitis in three children associated with 2009 influenza A(H1N1) virus infection. *Chest* **138**: 1486-1488, 2010.
3. Eberlein MH, Drummond MB, Haponik EF. Plastic bronchitis: a management challenge. *Am J Med Sci* **335**: 163-169, 2008.
4. Isobe M, Sasaki S, Hojo M, et al. A bronchial cast caused by pulmonary hemorrhage due to a vitamin K deficiency. *Pediatr Int* **53**: 133-134, 2011.
5. Coonar A. Blood clot cast of the bronchial tree. *Eur J Cardiothorac Surg* **28**: 490, 2005.
6. Morris LG, Sheu M, Zeitler DM. Blood clot cast of the tracheobronchial tree. *ANZ J Surg* **80**: 473-474, 2010.
7. Skatrud J, Gilbert R, Auchincloss JH Jr. Letter: Blood clot cast following hemoptysis and resulting in atelectasis. *Chest* **69**: 131, 1976.
8. Fujita J, Ohtsuki Y, Higa H, et al. Clinicopathological findings of four cases of pure influenza virus A pneumonia. *Intern Med* **53**: 1333-1342, 2014.
9. Mauad T, Hajjar LA, Callegari GD, et al. Lung pathology in fatal novel human influenza A (H1N1) infection. *Am J Respir Crit Care Med* **181**: 72-79, 2010.
10. Antoniak S, Tatsumi K, Hisada Y, et al. Tissue factor deficiency increases alveolar hemorrhage and death in influenza A virus-infected mice. *J Thromb Haemost* **14**: 1238-1248, 2016.
11. Aokage T, Palmér K, Ichiba S, Takeda S. Extracorporeal membrane oxygenation for acute respiratory distress syndrome. *J Intensive Care* **3**: 17, 2015.
12. Hayes RA, Shekar K, Fraser JF. Is hyperoxaemia helping or hurting patients during extracorporeal membrane oxygenation? Review of a complex problem. *Perfusion* **28**: 184-193, 2013.

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