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【 CASE REPORT 】

Venovenous Extracorporeal Membrane Oxygenation in Diffuse Alveolar Hemorrhage Secondary to Anti-neutrophil Cytoplasmic Autoantibody-associated Vasculitis: Starting without Systemic Anticoagulation

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Abstract:

Regarding extracorporeal membrane oxygenation (ECMO) support against hemorrhagic conditions, there seems to be a dilemma when deciding between maintaining the circuit patency by systemic anticoagulation and increasing the risk of bleeding. We herein report two cases of diffuse alveolar hemorrhage (DAH) caused by myeloperoxidase (MPO) anti-neutrophil cytoplasmic autoantibody-associated vasculitis (AAV) successfully treated with venovenous (VV)-ECMO support, both initially started without systemic anticoagulation. Under anticoagulation-free ECMO management, we should consider the shortcomings of frequent circuit exchange and hemorrhagic diathesis related to circuit-induced disseminated intravascular coagulation (DIC).

Key words: diffuse alveolar hemorrhage, myeloperoxidase anti-neutrophil cytoplasmic autoantibody-associated vasculitis, extracorporeal membrane oxygenation

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Introduction

Anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) is a disorder that predominantly affects small-to-medium-sized arteries, involving multiple organs with a common pathology and the presence of ANCA (1). Diffuse alveolar hemorrhage (DAH) is a prominent and life-threatening pulmonary manifestation of AAV and is estimated to occur in 5-45% of admitted patients (2). Its typical presentation includes the rapid onset of dyspnea progressing to respiratory failure, which may be catastrophic.

Several reports have described the benefits of performing venovenous-extracorporeal membrane oxygenation (VV-ECMO) for severe respiratory failure from DAH associated with AAV (3, 4). During ECMO, patients receive anticoagulants that help prevent thrombotic complications and maintain circuit patency, placing them at the risk of bleeding (5). In patients with active or a high risk of major bleeding, anticoagulation-free ECMO is an option, but the precise safety and efficacy are largely unknown (6).

We herein report two cases of myeloperoxidase (MPO)-AAV that were successfully treated with immunosuppressive therapies under ECMO initially without systemic anticoagulation.

Case Reports

Case 1 was a 70-year-old woman (height, 149 cm; body weight, 45 kg) with hypertension and dyslipidemia, who was brought to our department emergently for dyspnea. Two months prior to admission, she had experienced fatigue and anorexia.

Upon reaching our emergency room, her SpO_2 was 85% under 10 L/min of oxygen via a non-rebreather mask. Chest radiography and computed tomography revealed bilateral lung consolidations (Fig. 1). Bronchoscopy under intubation revealed extensive bleeding from both lungs, suggesting alveolar hemorrhage.

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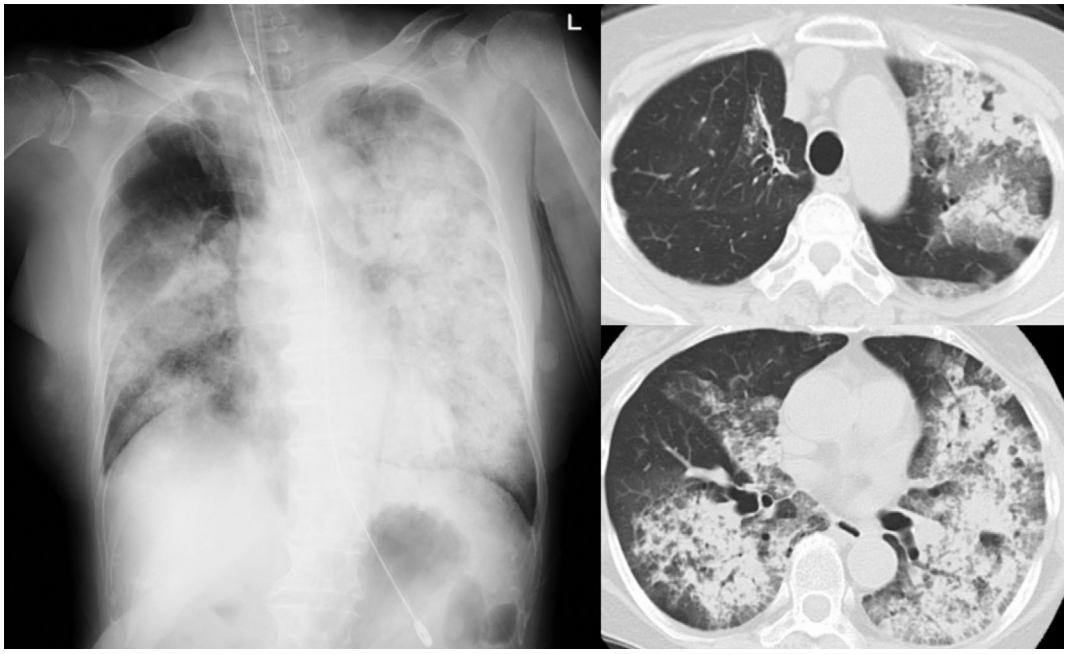

Figure 1. **Chest radiography and chest plain CT of case 1 on hospital day 1. Chest radiography shows bilateral consolidation. Chest plain CT shows diffuse consolidation with concomitant ground-grass opacities. CT: computed tomography**

Her laboratory data showed a low hemoglobin level of 4.4 g/dL and elevated creatinine level of 6.64 mg/dL, which was accompanied by proteinuria and hematuria, as suggested by the urine dipstick test. Reverse transcriptase polymerase chain reaction (RT-PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a nasopharyngeal swab was negative. Blood culture was negative, and sputum culture revealed only normal flora.

On hospital day 2, her hypoxemia and respiratory acidosis had deteriorated. Under a ventilator setting of positive end-expiratory pressure (PEEP) 10 cmH_2O and FiO_2 1.0, a blood gas analysis showed a pH of 7.076, PO_2 of 80.7 mmHg, and PCO_2 of 88.5 mmHg. We therefore decided to administer VV-ECMO support, composed of a Rotaflow system (Maquet, Rastatt, Germany) as the blood centrifugal pump and MERA NHP Exelung TPC HPO-23H-CP (Senko Medical Instrument, Tokyo, Japan) as the membrane oxygenator. Because of her hemorrhagic condition, ECMO was initially managed without systemic anticoagulation.

Serology exams showed positive results for MPO-ANCA on an enzyme-linked immunosorbent assay (ELISA; 281 U/mL), and a diagnosis of DAH and rapidly progressing glomerulonephtiris associated with MPO-AAV was made. She received a pulse dose steroid course (methylprednisolone 1,000 mg/day) for 3 days and underwent plasma exchange on days 2 and 3, followed by prednisolone (60 mg/day), intravenous cyclophosphamide (400 mg) on day 4, and rituximab therapy (375 mg/m^2) on day 5. The progression of anemia stabilized after the initial plasma exchange, so continuous heparin administration was initiated, with the target activated partial thromboplastin time (aPTT) set to twice the pre-heparin treatment value.

Neither hemorrhagic nor thrombotic complications were observed, and she was successfully weaned off of ECMO on day 7 and extubated on day 10. On day 96, the patient was discharged home.

Case 2 was a 63-year-old man (height, 166 cm; body weight, 74 kg) with a history of hypertension. He experienced antecedent symptoms of cough and shortness of breath, which progressed over two days, leading to ambulatory transport to our department. On arrival, he was desaturated with SpO_2 80% under 10 L/min of oxygen via a non-rebreather mask and showed marked respiratory effort, which required invasive mechanical ventilation.

A blood gas analysis under ventilator settings of PEEP at 12 cmH_2O and FiO_2 at 1.0 showed a pH of 7.291, PO_2 of 61.1 mmHg, and PCO_2 of 53.3 mmHg, so VV-ECMO support was initiated. Its configuration included a Rotaflow system (Maquet) as a blood centrifugal pump and MERA NHP Exelung TPC HPO-23H-CP (Senko Medical Instrument) as a membrane oxygenator. Concerning the bleeding condition, he was managed with heparin-free ECMO support.

His chest radiograph revealed bilateral lung consolidation, and bronchoscopy confirmed massive airway hemorrhage in both lungs (Fig. 2). Laboratory test results showed a low hemoglobin level of 8.1 g/dL and a slightly elevated serum creatinine level of 1.05 mg/dL as well as positive results for proteinuria and hematuria on the urine dipstick test. RT-PCR did not detect SARS-CoV-2 from a nasopharyngeal swab, and blood culture was negative, while sputum culture revealed only normal flora. Serology tests yielded positive results for MPO-ANCA on an ELISA (222 U/mL), and he was diagnosed with DAH associated with MPO-AAV.

He was started on VV-ECMO without anticoagulation and

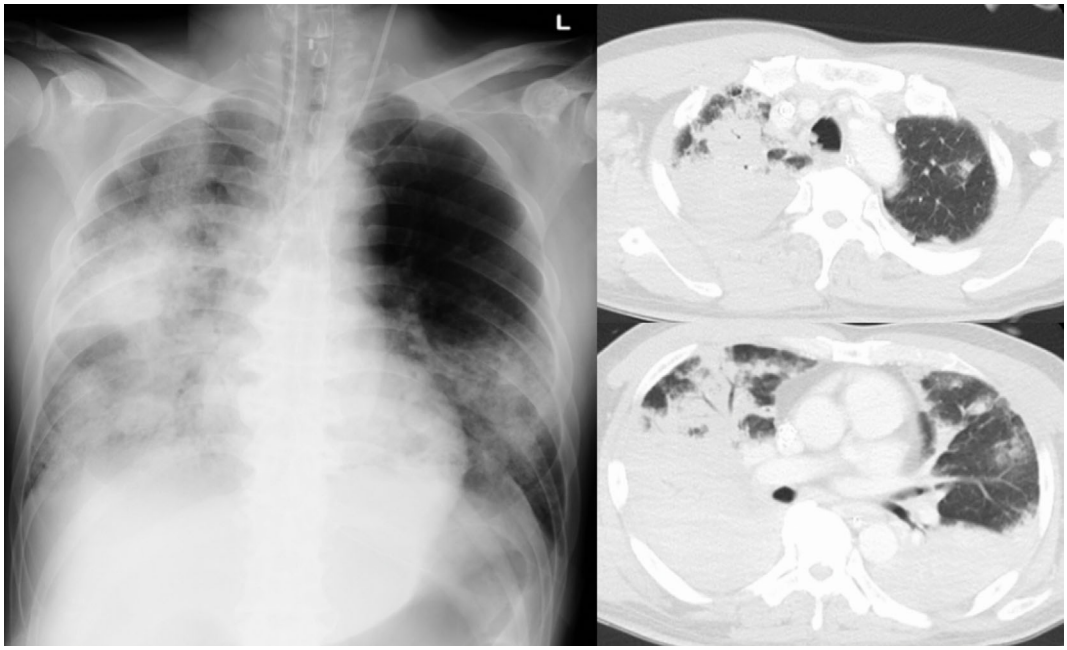

Figure 2. **Chest radiography and plain chest CT of case 2 on hospital day 1. Chest radiography shows bilateral consolidation predominating, which is predominant in the right lung. Chest plain CT shows consolidative or ground-grass opacities on ventral areas of the lungs, and consolidation without air bronchogram on dorsal areas of the lungs, which suggests obstruction of lower respiratory tract. CT: computed tomography**

with pulse dose methylprednisolone at 1,000 mg/day for 3 days, followed by methylprednisolone 80 mg/day, plasma exchange on day 4, and rituximab therapy (375 mg/m^2) on day 5. Hypoventilation was observed due to clot formation in the lower respiratory tract, and he required frequent aspiration by bronchoscopy. Clotting in the respiratory tract appeared to have peaked on day 6. Circuit exchange was conducted on hospital day 7 due to increasing thrombi formation in the oxygenator, although the gas exchange ability of the artificial lung was maintained according to a postmembrane blood gas analysis (PaO_2/FiO_2 ratio of 456). Although coagulation tests showed low fibrinogen (138 mg/dL) with elevated fibrin/fibrinogen degradation products (91.1 μg/mL) and D-dimer (43.3 μg/mL) levels, these parameters did not show a persistent trend, and on rotational thromboelastography (ROTEM®), which assesses in real-time both the kinetics and quality of clot formation, neither extreme prolongation of clotting time nor hyperfibrinolysis were observed (Fig. 3). On the same day, since no progression of anemia was seen and clot formation in the airway was apparently minimized, he was started on systemic anticoagulation with heparin, with aPTT maintained at twice the pre-heparin treatment value.

The patient's respiratory status showed gradual improvement, and ECMO was discontinued on day 12, followed by extubation on day 19. For further rehabilitation, the patient was transferred to another hospital on day 62.

Discussion

DAH has various causes, ranging from non-immune-mediated to immune-mediated etiologies, and the intensive-care unit mortality of patients with DAH related to autoimmune diseases is as high as 15% (7). It is one of the most catastrophic complications of AAV, and the related respiratory complaints may be the initial presentation of AAV. In some cases, only the lung capillaries seem to be affected ("isolated pulmonary capillaritis"), making it difficult to reach the correct diagnosis (8). Supporting these patients with VV-ECMO ensures sufficient time to make a definite diagnostic and initiate treatment measures, along with minimizing ventilator-associated lung injury. The Extracorporeal Life Support Organization's registry of patients with AAV on ECMO showed a 73% survival rate, and factors associated with death included an older age, use of venoarterial ECMO, ECMO-cardiopulmonary resuscitation, and sustaining cardiac arrest before ECMO (3).

Despite advances in devices such as heparin-coated ECMO circuits, cannulas, and biocompatible membranes, hemorrhagic complications are frequently seen in patients under VV-ECMO management, with up to 17% of complications directly contributing to mortality (9). Manufacturers recommend anticoagulation with heparin with an aPTT maintained at 1.5-2.5 times the baseline value, which is about 50-70 seconds, but ECMO therapy with a prolonged aPTT is known to be related to adverse hemorrhagic events. Minimizing the risk of bleeding is considered especially im-

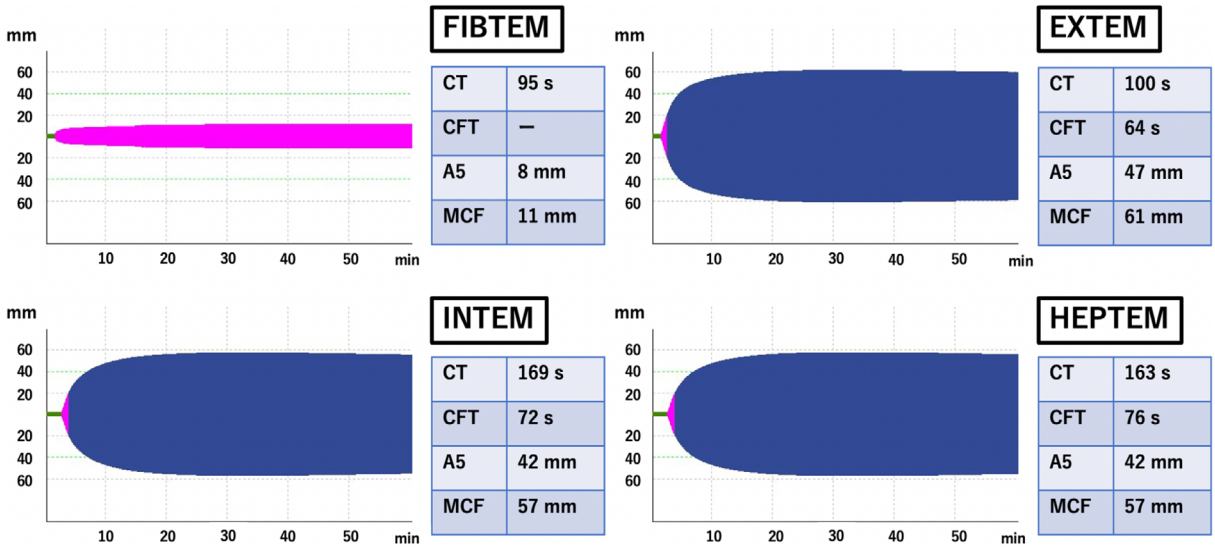

Figure 3. **ROTEM results of case 2 on hospital day 6. Constant rotational force is applied to a small sample of clotting blood, and changes in viscoelastic strength are transduced in real time, allowing visual assessment of blood coagulation from clot formation, through propagation, stabilization and clot dissolution. In EXTEM, which reflects coagulation activated by tissue factor, showed prolonged CT, but is sometimes seen on patients under ECMO management. Maximum lysis during runtime are within normal range on all assays. CT: coagulation time, CFT: clot formation time, A10: amplitude of clot firmness 5 min after CT, MCF: maximum clot firmness**

portant in cases of early post-traumatic or surgical patients, and there are reports of low-level and or delayed anticoagulation being used safely (10).

Anticoagulation-free ECMO is an option for cases with active or at a high risk of major bleeding, although data regarding the safety and efficacy of this approach are limited. The disadvantages of anticoagulation-free ECMO include the need for frequent circuit exchange, and increased concerns about ECMO-associated coagulopathy (EACP), which can paradoxically allow the patient to develop hemorrhagic diathesis. EACP seems to have multifactorial cases; not only artificial surfaces and shear stress inside the ECMO system, but also pre-ECMO conditions such as acute respiratory distress syndrome (ARDS), heart failure and hepatic dysfunction, or hemodilution that lead to aggravation of plasmatic coagulation disturbances on ECMO initiation contribute to the progression of EACP (11). In a systematic review of 154 patients who underwent ECMO without therapeutic-dose systemic anticoagulation, the rates of systemic venous or arterial thrombosis and severe bleeding events were 3.9% and 8.4%, respectively, and no intracranial hemorrhage was observed in the latter (6, 10).

Regarding AAV associated with DAH, we could only find a single case report of anticoagulant-free VV-ECMO management of AAV complicated with DAH and bowel bleeding (12). There have been reports of successful VV-ECMO treatment for AAV with systemic anticoagulation without exacerbation of pulmonary bleeding (4, 13).

For both ECMO configurations in our patients, we chose MERA NHP Exelung TPC HPO-23H-CP (Senko Medical Instrument) as the membrane oxygenator. It is a hollow fiber membrane made of polypropylene and a silicone layer on the outer surface, coated with heparin compound. In case 1, while we initiated anticoagulation with heparin, targeting an aPTT of about twice the pre-heparin value on the same day when ECMO support was started, the patient successfully underwent initial definite treatment as well as completion of VV-ECMO support. Difficulties related to circuit patency, such as thrombosis and hemorrhagic complications, were documented. In contrast, the patient in case 2 underwent anticoagulation-free VV-ECMO for 7 days, due to extensive hemorrhage and clot formation in the airways, which seemed more aggressive than that seen in case 1. Although the ECMO circuit exchange was performed because of extensive thrombi formation on the ECMO oxygenator, its gas exchangeability seemed to be preserved. The patient was successfully weaned from ECMO support without sequelae.

An appropriate anticoagulation strategy for ECMO against internal hemorrhagic complications, such as DAH, has yet to be established. Taking our experience into account, ECMO management starting with no systemic anticoagulation may be a useful option, provided that the clinicians and staff are cautious of the risk of frequent decline in circuit patency and of the increasing risk of ECMO-associated coagulopathy.

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

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