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Successful Treatment of Panton-Valentine Leukocidin-expressing *Staphylococcus aureus*-associated Pneumonia Co-infected with Influenza Using Extracorporeal Membrane Oxygenation

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Abstract. *Background: Panton-Valentine leukocidin (PVL) is a cytotoxin that causes leukocyte destruction and lung necrosis. Managing respiratory failure and acute respiratory distress syndrome secondary to PVL-expressing Staphylococcus aureus pneumonia and its associated lung necrosis with mechanical ventilation is challenging. We report a patient with life-threatening PVL-expressing S. aureus-associated pneumonia who was rescued using extracorporeal membrane oxygenation (ECMO). Case Report: We examined the case of a woman who presented to our Emergency Department with septic shock due to PVL-expressing S. aureus-associated pneumonia. A 27-year-old Filipino woman was transferred to our hospital due to severe dyspnea, hemosputum, and high-grade fever. She had a medical history of osteosarcoma of the leg and hyperthyroidism. On arrival, her vital signs indicated septic shock, with a white blood cell count of $3.5\times10^3/\mu l$. Because a Gram stain of her sputum indicated SA, therapy with antibiotics, including meropenem and vancomycin, was started. Hypoxemia necessitated intubation and ventilation. Because the patient's PaO_2/FiO_2 remained less than 60 mmHg and her blood pressure was unstable despite aggressive conventional management, venoarterial ECMO was administered approximately 11 h after her arrival. The ECMO circuit was changed to veno-venous ECMO on day 7 and the patient was successfully weaned off ECMO after 12 days of treatment. She was discharged from the hospital 104 days after admission. Conclusion: This case demonstrates that early induction of ECMO support can be a reasonable therapeutic option for PVL-S. aureus-associated pneumonia. This patient's successful outcome might be attributable to early establishment of ECMO to prevent ventilation-induced lung injury.*

Staphylococcus aureus, a major cause of infectious disease, is responsible for at least 10% of nosocomial pneumonia cases but only 2% of community-acquired pneumonia cases (1, 2). There are various *S. aureus* virulence factors, including hemolysins and leukocidins. A very small minority of *S. aureus* strains carry Panton-Valentine leukocidin (PVL), a pore-forming cytotoxin that causes leukocyte destruction and lung necrosis. PVL has been associated with diverse clinical syndromes characterized by abscess formation, cavitation, hemorrhage, necrosis, and mortality approaching 75% (3). In particular, secondary respiratory failure and acute respiratory distress syndrome (ARDS) due to PVL-expressing *S. aureus*-associated pneumonia and consequent lung necrosis are challenging to manage with mechanical ventilation. ARDS associated with PVL-*S. aureus*-associated pneumonia has a mortality rate of over 70% despite aggressive management with multiple antibiotic combinations (4).

We report a patient with life-threatening PVL-expressing, methicillin-susceptible *S. aureus*-associated pneumonia co-infected with influenza type A who was rescued using extracorporeal membrane oxygenation (ECMO). Our patient presented with respiratory failure which could not be managed with various interventions, including ventilation. Although ECMO for PVL*S. aureus*-associated pneumonia has largely been unsuccessful (5, 6), our experience may add another encouraging, successfully-treated case of necrotizing pneumonia to previous reports, suggesting that ECMO may be a useful therapeutic tool for PVL-*S. aureus*-associated pneumonia (7, 8).

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Case Report

A 27-year-old Filipino woman was transferred to our Hospital due to severe dyspnea. She presented flu-like symptoms: fatigue, hemosputum, sore throat, and high-grade fever starting the day before visiting our hospital. She had a medical history of surgery for right hip disarticulation due to osteosarcoma and untreated hyperthyroidism. Her vital signs at time of arrival were as follows: blood pressure 77/28 mmHg; pulse rate 178 beat per minute; temperature 39.8˚C, 51 respirations per minute, and 90% oxygen saturation using a 10 l oxygen mask with the reservoir. Physical examinations showed obvious exophthalmos and coarse crackles were heard in all bilateral lungs fields. Tests for hepatitis type B and type C, and human immunodeficiency virus were negative. Laboratory data revealed a white blood cell count of 3.5×10^3/μl and C-reactive protein level of 18.97 mg/dl, and arterial blood gas analysis demonstrated hypoxia, pH: 7.393, Partial pressure of oxygen: 58.8 mmHg, Partial pressure of carbon dioxide: 34.8 mmHg, bicarbonate: 20.8 mmol/l, and Base excess: −3.0 mEq/l. Acute respiratory failure prompted intubation and ventilation. Chest radiography showed bilateral alveolar infiltrates and nodular change mainly on the right side. Nasopharyngeal aspirate was positive for influenza type A. In addition, Gram stain of her sputum revealed *S. aureus*. Treatments, including those with meropenem, vancomycin, oseltamivir, and immunoglobulin, were started for septic shock due to community-acquired pneumonia as a secondary complication of influenza infection. Since thyroid storm was also suspected, hydrocortisone and β-blocker were administered at the same time.

The patient's PaO_2/FiO_2 ratio remained at around 60 despite aggressive conventional management with airway pressure release ventilation or assist control. As prolonged hypotension persisted despite noradrenaline use, venoarterial (VA) ECMO was instituted through the left femoral artery and right femoral vein approximately 11 hours after the patient's arrival. Lung protection was difficult to establish due to severe hypoxemia. Ischemic symptoms were seen in the left lower extremity on the second day of illness. An arterial catheter was inserted toward the distal extremity to start peripheral perfusion. Clindamycin was added because of its advantage of switching off toxin production. On the third day, laboratory data showed rapidly progressing acute kidney injury with a creatine kinase increase of about 60,000 units; continuous hemodiafiltration was promptly inducted. Antibiotics were changed to cefazolin and clindamycin because her sputum and blood cultures yielded methicillin-sensitive *S. aureus*. On day 5, the methicillin-sensitive *S. aureus* was proven to be a PVL-positive strain. On day 7, the VA ECMO circuit was changed to veno-venous (VV) ECMO that was instituted through the right jugular vein and right femoral vein. The patient recovered from septic shock through use of cefazolin, meropenem, linezolid, and micafungin on day 9, and the patient was successfully weaned from VV ECMO after 12 days of treatment. No remarkable trouble was encountered while running VV ECMO. On day 29, continuous hemodiafiltration was completed and hemodialysis was performed every other day. On day 30, tracheostomy was performed. The patient was transferred from the intensive care unit to the medical ward on day 41 and was finally successfully weaned off mechanical ventilation after 52 days (Figures 1 and 2). She was discharged from the hospital 104 days after admission.

Discussion

Since Lina *et al.* first described an association between necrotizing pneumonia and PVL-secreting pneumonia in 1999 (9), an increasing number of PVL-*S. aureus*-associated pneumonia cases have been reported. However, the true incidence of PVL-associated pneumonia is unknown, as the number of published cases is likely underestimated and cases may go unrecognized. PVL is generally more often detected in community-acquired methicillin-resistant *S. aureus* than in methicillin-susceptible *S. aureus* (10). Patients with PVL-positive samples tend to be young and have no remarkable risk factors. Mortality rates also significantly differ between the two types: PVL-positive infection has a higher mortality rate than PVL-negative infection (11). Currently, no evidence-based guidelines for management of PVL-*S. aureus*-associated pneumonia exist (4).

Although primary infection can occur in young, fit, immunocompetent patients, increasing evidence suggests that PVL-*S. aureus*-associated pneumonia may occur secondary to influenza infection, raising concern about possible PVL-*S. aureus*-associated pneumonia outbreaks during influenza epidemics (12). Although the mortality rate for *S. aureus*-associated pneumonia in general is about 10%, PVL-*S. aureus*-associated pneumonia can cause severe, necrotizing pneumonia associated with ARDS, which can be particularly challenging to manage.

Current management modalities include high-frequency oscillatory ventilation, exchange blood transfusion, nitric oxide therapy, and ECMO, in conjunction with various antibiotic combinations. Antibiotics protocols are still under debate. Some reports describe β-lactam as worsening respiratory function and pulmonary infiltrates, whereas clindamycin, linezolid and daptomycin play a role in preventing toxin production. We chose cefazolin because of its high sensitivity and clindamycin for its ability to prevent toxin production. The treatment response was good. Because a rash appeared on her whole body, clindamycin was replaced with continuous linezolid for antitoxin treatment. When treating fatal *S. aureus*-associated pneumonia, not only selecting appropriate antibiotics but also combining them

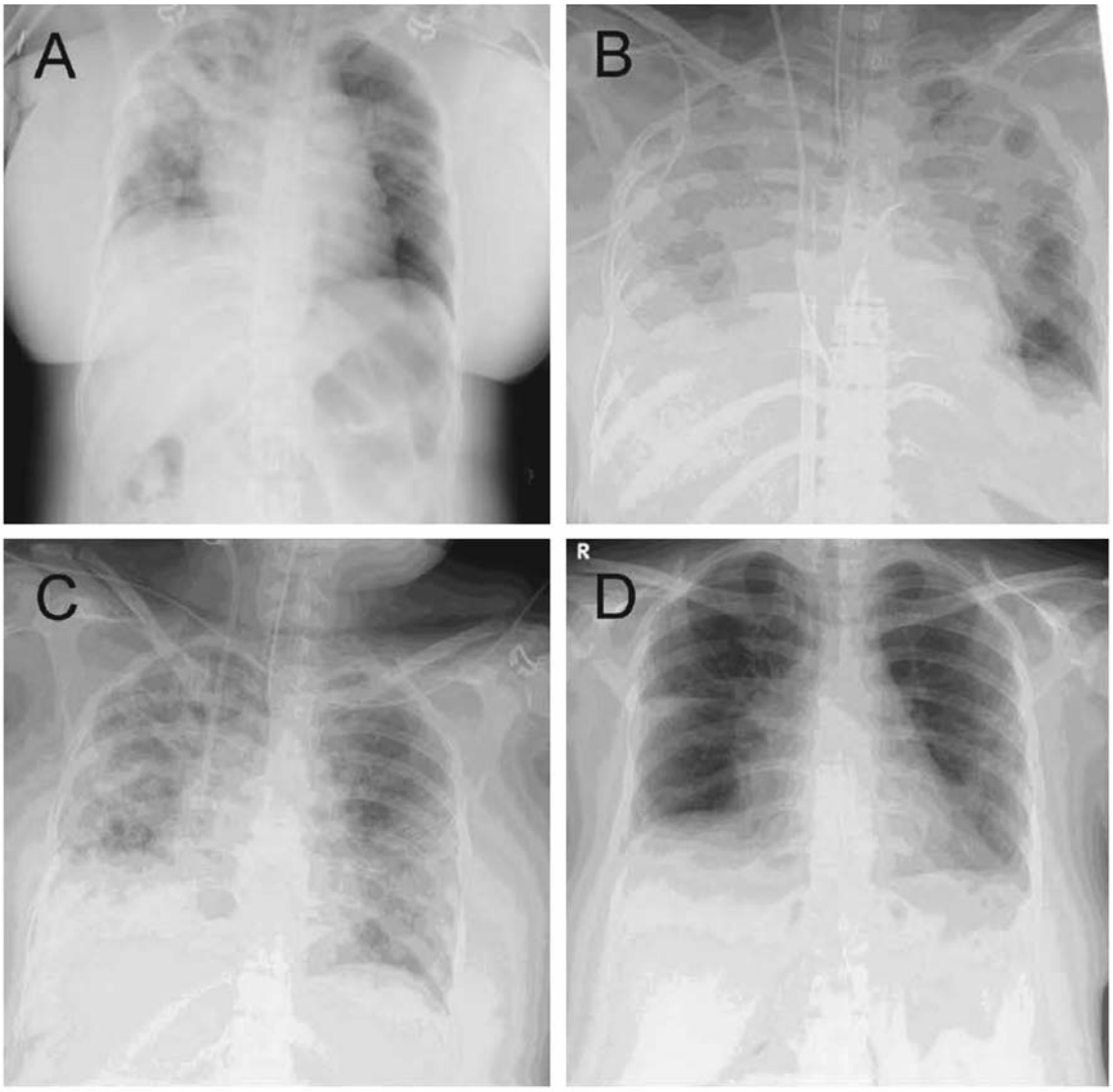

Figure 1. *A: Chest radiograph at admission showed bilateral alveolar infiltrates and nodular change mainly on the right side. B: Chest radiograph 11 h after admission, after induction of venoarterial extracorporeal membrane oxygenation. C: Chest radiograph taken after weaning from venovenous extracorporeal membrane oxygenation at day 12. D: Chest radiograph on day 71.*

with antitoxic agents and immunoglobulin without delay is of the utmost importance (13, 14). Intravenous immunoglobulin (IVIg) neutralizes PVL pore formation and the cytopathic effects of PVL *in vitro* (15), although the optimal IVIg dosage is uncertain. IVIg has been used in patients with PVL-associated pneumonia (5). Granulocyte colony-stimulating factor has also been used in neutropenic patients with necrotizing pneumonia (7).

After the Conventional Ventilation or ECMO for Severe Adult Respiratory Failure trial, ECMO was recognized as an effective technique to treat acute respiratory failure, especially for patients with severe pulmonary conditions thought to be pathophysiologically reversible (16). ECMO support permits low-pressure lung ventilation, avoiding varotrauma or ventilation-induced lung injury to lungs made friable by PVL-*S. aureus* infection. Respiratory management during ECMO recommends 'lung rest' and ventilation with low inspiratory pressure; a low FiO_2 is possible while performing ECMO.

Very little information is provided in the literature about management of patients with PVL-*S. aureus*-associated pneumonia with ECMO support. However, we decided to start VA ECMO for the prolonged septic shock. Although our patient did not present respiratory acidosis, causing

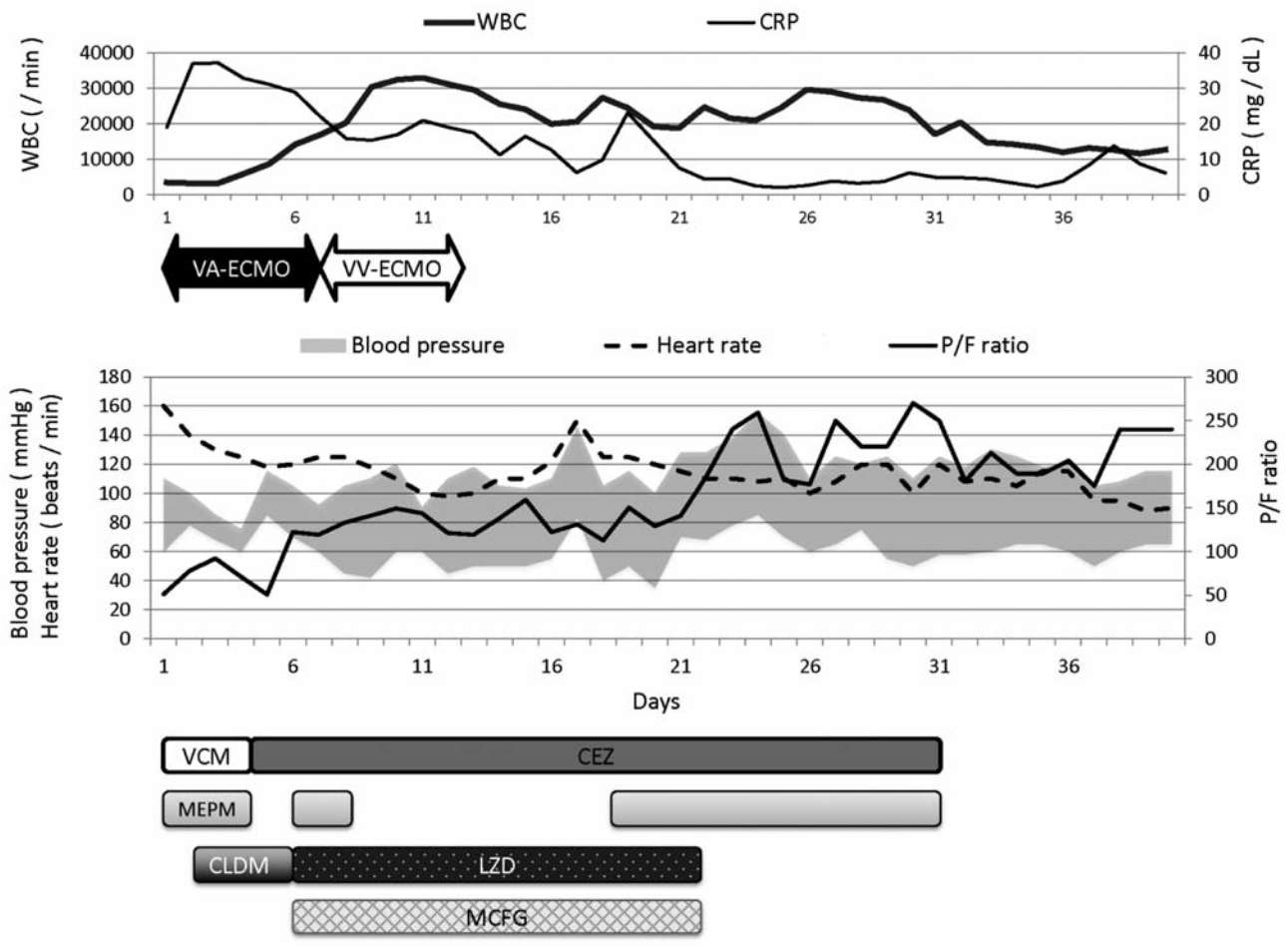

Figure 2. *Detailed follow-up and treatment until leaving the Intensive Care Unit are shown. The upper record shows the change of white blood cell count and C-reactive protein. The middle record show the progress of blood pressure, heart rate and PaO_2/FiO_2 ratio (P/F) ratio. The lower record shows the change of antibiotic treatment. VA ECMO: Venoarterial extracorporeal membrane oxygenation, VV ECMO: venovenous extra corporeal membrane oxygenation, P/F ratio: VCM: vancomycin, CEZ: cefazolin, MEPM: meropenem, CLDM: clindamycin, LZD: linezolid, MCFG: micafungin.*

progressive and irreversible lung injury without immediate induction of ECMO was possible (Murray score of 3.5) (17).

Conclusion

We herein presented our experience using ECMO to manage a patient with PVL-*S. aureus*-associated pneumonia. Necrotizing pneumonia due to community-associated *S. aureus* is increasingly reported in otherwise healthy individuals. This case demonstrates that early induction of ECMO support can be a reasonable therapeutic option for PVL-*S. aureus*-associated pneumonia. Although further studies based on larger patient cohorts are necessary to confirm our findings, the successful outcome in this patient may imply that early establishment of ECMO significantly prevents ventilation-induced lung injury.

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