Treatment of Sepsis and ARDS With Extracorporeal Membrane Oxygenation and Interventional Lung Assist Membrane Ventilator in a Patient With Acute Lymphoblastic Leukemia

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We report an 18-year-old ice skater with acute lymphoblast leukemia. She developed *Staphylococcus epidermidis* bacteremia, severe sepsis, septic shock, and ARDS following chemotherapy-induced severe bone marrow failure. She was successfully treated with extraordinary life support measures, which included extracorporeal membrane oxygenation, double lumen lung ventilation for management of hemoptysis, and lung assist membrane ventilation. After 57 days of ICU treatment and a year of rehabilitation, the patient has fully regained her functional status, is now finishing high school, and is ice skating again. *Key words: extracorporeal membrane oxygenation; interventional lung assist membrane ventilator; acute lymphoblast leukemia.* [Respir Care 2012;57(7):1178–1181. © 2012 Daedalus Enterprises]

Introduction

Extracorporeal life support remains a controversial therapy in the management of patients with severe refractory oxygenation failure, but has been successfully used as salvage therapy. Immunosuppression and coagulopathies are known contraindications for extracorporeal life support. We report a patient with acute lymphoblast leukemia, who developed mediport associated *Staphylococcus epidermidis* bacteremia following chemotherapy. She developed refractory oxygenation failure, septic shock, and severe hemorrhagic shock. She was maximally resuscitated with extracorporeal membrane oxygenation (ECMO), multiple units of blood product transfusion, differential lung ventilation, and lung assist membrane ventilation. With institution of extraordinary life support she had a successful outcome and she regained her full pre-morbid function status.

Case Report

An 18-year-old ice skater was diagnosed with acute lymphoblast leukemia. She received 3 cycles of chemotherapy (combination of doxorubicin and vincristine) via tunneled mediport inserted into the subclavian vein. She developed central line associated *S. epidermidis* bacteremia associated with septic shock and ARDS. The patient was initially hospitalized in a remote ICU. The culprit of the sepsis was *S. epidermidis*, isolated from 4 blood cultures and from the tip of the subclavian port, which was subsequently removed. Laboratory findings showed pancytopenia (red blood cells 2.95×10^6 cells/μL, white blood cells 0.2×10^3 cells/μL, platelets 13×10^3 cells/μL), elevated inflammatory parameters (C-reactive protein 273 mg/L, procalcitonin 14.49 μg/L), signs of liver failure (aspartate aminotransferase 570.59 U/L, alanine aminotransferase 644.71 U/L, lactate dehydrogenase 1929.41 U/L, gamma-glutamyl transpeptidase 176.47 U/L, alkaline phosphatase 141.18 U/L), coagulopathies (prothrombin time 0.42 s, international normalized ratio 1.72 s, activated partial thromboplastin time 72.5 s), and increased N-terminal pro-brain natriuretic peptide of $>$ 35,000 pg/

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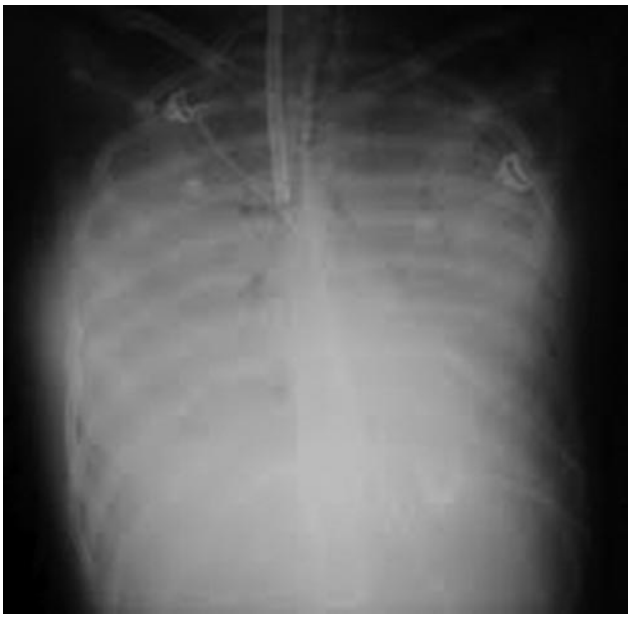

Fig. 1. Chest x-ray at the beginning of treatment.

mL. In spite of immediate empiric antimicrobial therapy with piperacillin/tazobactam, which was subsequently substituted for imipenem/cilastatin, vancomycin, and gentamicin, her condition deteriorated. Lung infiltrates, which were initially apparent in the right upper lobe, spread to both lungs (Fig. 1). She was intubated and mechanically ventilated. She remained persistently hypotensive, with blood pressure of 70/30 mm Hg, despite maximal vasopressors and inotropes (noradrenaline 1.5 μg/kg/min, vasopressin 1.6 IE/h, dobutamine 16 μg/kg/min). Echocardiography revealed dilated right ventricle with decreased contractility, and moderately diminished left ventricular ejection fraction of 35%. Conventional mechanical ventilation[1] with 100% oxygen and inhaled nitric oxide, as well as high frequency oscillatory ventilation, failed to maintain adequate arterial oxygenation and ventilation (pH 7,19, P_{CO_2} 65.2 mm Hg, P_{O_2} 48.0 mm Hg, S_{pO_2} 76%). On day 5, veno-venous ECMO was percutaneously inserted (Levitronix CentriMag, Thoratec, Pleasanton, California, with Hilite 7000 membrane, Medos Medizintechnik, Stolberg, Germany), using femoral and jugular vein access. With 3,700 rotations/min, minute blood flow of 4.5 L/min, F_{IO_2} of 0.7, and sweep gas flow of 2.5 L/min, hemodynamic and respiratory stabilization was achieved, and the patient was subsequently transferred to the ECMO center.

Veno-venous ECMO allowed us to use ultraprotective pressure controlled ventilation[2] with peak pressure of 30 cm H_2O, PEEP of 15 cm H_2O, ventilation frequency of 12 breaths/min, and F_{IO_2} of 0.3. A continuous infusion of unfractionated heparin was started to maintain an activated partial thromboplastin time between 50 and 70 s. On day 12, diffuse gastrointestinal bleeding, left lung hemorrhage, and bleeding at the puncture sites occurred and resulted in severe hemorrhagic shock. Heparin was discontinued and she received the following blood products: 165 units of packed red blood cells, 102 units of platelets, 120 units of fresh frozen plasma, one prothrombin complex, one concentrate of antithrombin III, and 18 applications of activated factor VII. Because of continuous bleeding from the left lung, a double lumen endotracheal tube was inserted to isolate the left lung and prevent aspiration of blood into the right lung. She was placed on differential lung ventilation. Tracheotomy was also done. With gradual recovery of the bone marrow, the bleeding ceased and hemostasis normalized. Along with the previously described coagulation tests, rotation thrombelastometry was used on daily basis, and heparin infusion was slowly reinstituted.

Despite 35 days of ECMO, the membrane was changed only 3 times. After gradual recovery of lung function, we weaned her from ECMO, which was discontinued on day 47. Despite adequate oxygenation using conventional ventilation with F_{IO_2} of 0.5, hypercapnia with development of respiratory acidosis (pH 7.19, P_{CO_2} 101.6 mm Hg, HCO_3 289.5 mEq/L) developed. That led us to institute interventional lung assist membrane ventilator (Novalung, Novalung, Heilbronn, Germany)[3] to facilitate CO_2 removal. Cannulation of the left femoral artery and the right femoral vein were therefore performed. After 10 days, interventional lung assist membrane ventilator could be discontinued, and the patient was successfully weaned from mechanical ventilation 20 days later (Fig. 2). After 57 days of ICU treatment and a year of rehabilitation, the patient is now finishing high school and ice skating again. Acute lymphoblast leukemia is in clinical remission on maintenance chemotherapy after one year. Her spirometry one year after discharge from hospital showed normal values.

Discussion

Previous reports have shown substantial benefit of ECMO in critically ill patients with severe respiratory failure. ECMO is a salvage therapy, and allows for ultraprotective ventilation, which minimizes ventilator associated lung injury and enables injured lung parenchyma to heal.[4]

The patient could not be transported immediately to an ECMO center because of unstable clinical status. The only option was cannulation and start of ECMO in the ICU where the patient was initially hospitalized. It is important to emphasize that cannulation by experienced doctors and hemodynamic and respiratory stabilization prior to transport is likely to increase survival of such patients.[5] Transportation of our patient to an ECMO center was therefore performed only after prior stabilization.[4]

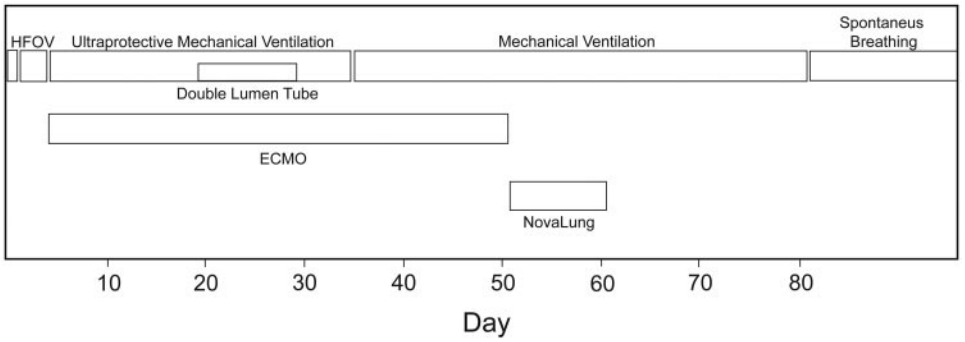

Fig. 2. Timeline of ventilatory support. ECMO = extracorporeal membrane oxygenation.

ARDS and severe septic shock resistant to conventional treatment left us with ECMO as the only remaining option to keep the patient alive. Depressed cardiac function was probably related to sepsis, hypoxemia, and acidosis.[6,7] Doxorubicin toxicity to the heart was less likely because of predominantly right heart involvement and moderately diminished left ventricle ejection fraction, which is atypical for this drug.[8] This assumption was further supported by gradual and complete resolution of cardiac function. However, we did not perform right heart catheterization, which would allow estimation of right sided pressures and thereby a possible cardiac component responsible for acute respiratory failure. Despite obvious contraindications for ECMO, including hemorrhagic diathesis and immunosuppression,[9] we used this method because of age, good prognosis of primary disease, and a single report of successful extracorporeal life support in leukemic children.[10] Because of expected reversibility in myocardial depression, from the start we decided for less invasive veno-venous ECMO.

Immunosuppression can further threaten a patient on ECMO by new septic episodes. To prevent such complications, several protective measures were performed. The patient was in an isolation room with limited personnel access. Clinical examinations and laboratory testing were performed regularly for early detection of new infections, as well as frequently taken samples for microbiological examination from every potential source of infection. Bronchoalveolar lavages were performed for clearing the airways and collecting microbiological specimens. She received broad spectrum antimicrobial therapy, which was changed after a time in order to prevent the growth of resistant microorganisms.[11]

Hemorrhagic diathesis was related to previously described heparin treatment and vulnerable mucosal membranes, combined with bone marrow suppression, liver failure, and consumption of clotting factors, with activation of fibrinolysis as a consequence of the foreign body surface of the extracorporeal membrane.[12] Several massive hemorrhagic episodes occurred and were successfully controlled by using interventional procedures (bronchoscopy, gastroscopy), blood products, clotting factors, and discontinuation of heparin. The latter proved to be safe in a bleeding patient on ECMO if achieving sufficient cardiac output through a heparin-coated circuit. In such cases, thrombotic complications are adequately prevented until bleeding resolves.[12]

Veno-venous ECMO allowed the use of ultraprotective ventilation of injured lung.[2] Besides ventilator strategies, additional pharmacological therapy, in the form of inhaled nitric oxide (15–30 ppm), and conservative fluid management was used. Gradual recovery of the right side of the lung occurred. However, because of frequent endobronchial bleeding, especially in the left lung, a double lumen endotracheal tube was inserted. It allowed for separate ventilation of each lung, daily bronchoalveolar lavage, and prevented blood going from one lung to another.[13] Although both ventilator settings were the same, the tidal volumes were different because of a different amount of functional lung parenchyma.[14] The patient was intubated with a double lumen tube for 13 days, and afterwards a classical intubation was performed again because of decubitus of the carina and left main bronchus. Meanwhile, the left lung also partially recovered. The use of a double lumen tube, therefore, not only prevented blood spillage from one lung to the other, but also allowed each part of the lung its own pace of recovery.

After 47 days on ECMO, while sufficient oxygenation of arterial blood was achieved with an F_{IO_2} of 0.5 on mechanical ventilation, high dead-space ventilation resulted in persistent hypercapnia with respiratory acidosis and hemodynamic instability. We decided to use a less invasive step-down approach with interventional lung assist membrane ventilator.[2] Interventional lung assist membrane ventilator avoids pump-related complications, reduces blood contacting foreign surfaces, and simplifies clinical management.[3] During ICU stay the patient continuously received intensive physiotherapy that accelerated her recovery, and continued after discharge from the hospital.

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