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Pneumonia clinical reports

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Mechanical ventilation associated pneumonia during ECMO therapy. A challenge for the Intensive Care physician

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Sir,

We present the clinical case of a young patient who suffered from SARS-CoV-2 pneumonia, which required veno-venous ECMO, and was complicated by fatal nosocomial pneumonia associated with mechanical ventilation.

This is a 33-year-old patient with a history of systemic erythematosus lupus (SEL) and bronchial asthma, for which she was receiving home treatment with prednisone, colchicine, beclomethasone-formoterol, and salbutamol. At that time, not vaccinated against SARS-CoV-2.

The patient had a non-productive cough, dyspnea and fever, so a week after the onset of the symptoms, a PCR for SARS-CoV-2 was determined, which resulted positive. After a torpid evolution at home, one week later (14 days from the start of the symptoms) she was admitted to the Internal Medicine hospitalization ward of her reference hospital. Upon admission, treatment was started: remdesivir (for 10 days), dexamethasone (8 mg for 5 days and 20 mg for a further 5 days), tozilizumab (2 doses of 600 mg), as well as empirical antibiotic therapy with ceftriaxone and azithromycin (hours after the admission, the *S. pneumoniae* and *L. pneumophila* antigenuria were negative, so the aforementioned treatment was interrupted). In addition, intermediate doses of enoxaparin (1 mg/kg/day) and oxygen therapy in nasal cannulas were prescribed. After 4 days of hospital stay, and despite the measures, she presented further clinical deterioration, requiring high-flow nasal oxygen therapy, which is why she was admitted to the Intensive Care Unit (ICU) of the aforementioned hospital. The patient worsened and did not tolerate non-invasive mechanical ventilation, and after 4 days of stay in the ICU, intubation and invasive mechanical ventilation were performed. Despite ventilation, the situation of refractory hypoxemia persisted, even to prone maneuvers and lung recruitment. With a pO2/fiO2 ratio of 72 mmHg on the third day of invasive ventilation, we were consulted and the ECMO team from our hospital was moved to establish femoro-femoral veno-venous extracorporeal therapy (cardiac function resulted normal by echocardiography). After that, she was transferred by medicalized ambulance to our hospital (distance: 206 km). During the days after the extracorporeal circulation was initiated, protective lung ventilation was possible, maintaining a control pressure of 15 cmH2O, PEEP of 10 mmHg, respiratory rate between 10-12 breaths/min, and FiO2 of 60%. The chest X-ray showed a bilateral alveolar and interstitial pattern with bibasal pleural effusion (virtually a "bilateral white lung").

On the fifth day of ECMO care, the patient presented a low-grade fever of 37.7ºC (the extracorporeal device had a temperature control system incorporated), which was accompanied by a rise in the biomarkers (procalcitonin from 0.05 to 1.4 ng/ml and C-reactive protein: from 9 to 74 mg/l), leukocytosis with neutrophilia as well as increased quantity and purulence of respiratory secretions. Chest ultrasound revealed a consolidated lung parenchyma from upper to lower fields, with subpleural nodules and bilateral pleural effusion. Two diagnostic and therapeutic thoracocentesis were performed (no empyema), microbiological cultures were performed and meropenem and linezolid were empirically added due to the suspicion of mechanical ventilation associated pneumonia. Both the respiratory sample and the blood cultures grew *Pseudomonas aeruginosa*, vulnerable to ceftolozane/tazobactam and ceftazidime/avibactam, as well as to aminoglycosides and colistin, being resistant to meropenem. Antibiotic therapy was adjusted: meropenem was suspended and ceftazidime/avibactam was added (ceftolozane/tazobactam was not available).

After a few days of clinical stability, marked by dependence on extracorporeal support for oxygenation, a radiological improvement being able to maintain the range of ventilatory pressures at 15 cmH2O and without requiring vasoactive/inotropic drugs to maintain adequate blood pressure, on day 19 of Extracorporeal assistance the patient presented a se-

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rious deterioration of the ventilatory function, which forced to increase the blood flow by ECMO (75-80% of the patient's cardiac output), to carry out ventilation in prone position (up to 5 cycles) as well as to start nitric oxide therapy (up to 20 ppm). At that time, the Herpes virus type 1 was detected in the respiratory secretions (not fungi), and in both respiratory secretions and blood cultures, the sensitivity pattern of Pseudomonas aeruginosa (which continued to grow significantly) changed: it became vulnerable only to colistin, tobramycin, aztreonam-avibactam and cefiderocol. After directed antibacterial adjustment (intravenous and inhaled in a different combination of antibiotics with demonstrated sensitivity), on day 34 of ECMO care the patient progressed to a situation of septic shock of respiratory origin that required starting, in addition to vasoactive drugs at maximum doses, continuous venovenous hemodiafiltration at high flow (coupled to ECMO). Despite the extracorporeal oxygenation therapy and the adjustments in mechanical ventilation, dynamic compliance was less than 10 mL/cmH2O at all times and the pO2/fiO2 ratio was only 50-75 mmHg. Echocardiography revealed a hyperdynamic pattern at that time, and chest X-ray revealed pulmonary cavities in the upper lobes and middle lobe with complete consolidation of the rest of the lung parenchyma. Nevertheless, three days later the hemodynamic situation improved, the dose of vasopressors could be reduced, peripheral perfusion returned to normal status (lactate in the normal range) with no signs of ventricular dysfunction by echocardiography. However, severe respiratory dysfunction persisted, with extreme difficulty in ventilation performing (tidal volumes less than 100 ml). Despite to optimizing PEEP, performing cleaning fiberoptic bronchoscopy and attending the 90% of cardiac output by extracorporeal oxygenation, the pO2/fiO2 was only 50 mmHg (dynamic compliance 4 ml/cmH2O). In this situation, the patient was transferred to Radiology department and a chest CT scan was performed (Figure 1): it showed pulmonary cavities, which were large in both upper lobes (11 cm in the left) and in the middle lobe, with air-fluid levels, probably due to necrosis of the parenchyma and communication with the airway (less probably pneumatoceles). In addition, multiple small bilateral cystic lesions were identified, which could correspond to pneumatoceles or bronchial cystic dilatations, with complete consolidation of the pulmonary parenchyma.

On the 39th day of care, hemodynamic instability occurred again and the echocardiography showed an acute dilatation of the right ventricle, in addition to severe tricuspid regurgitation, whose gradient allowed estimating a systolic pulmonary arterial pressure of 80 mmHg. In this scenario of claudication of the right ventricle and refractory hypoxemia, it was decided to change the configuration to veno-arterial (femoro-axillary) ECMO, but despite the measures, multi-organ failure occurred and finally the patient death after 42 days of ECMO support.

In the current pandemic context, the main international organizations, including the World Health Organization, the Surviving Sepsis Campaign or the Extracorporeal Life Support Organization (ELSO), recommend the use of ECMO therapy in acute respiratory distress syndrome (ARDS) associated with

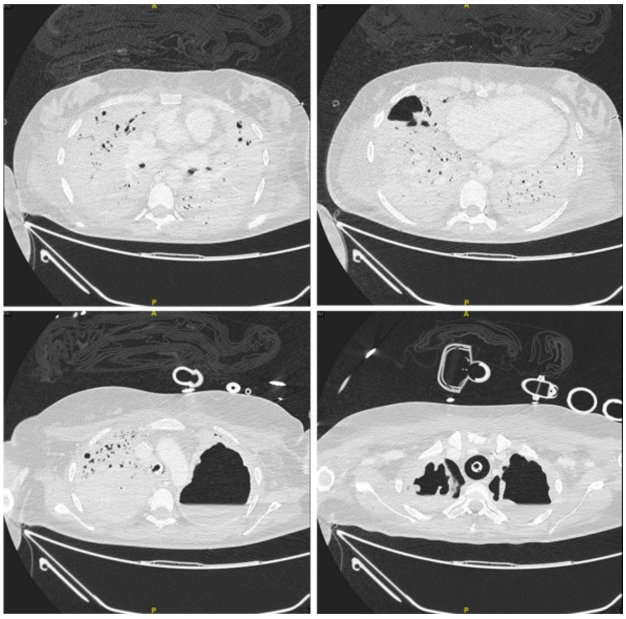

Figure 1 | **Chest CT scan**

COVID-19 presenting with hypoxemia refractory to conventional mechanical ventilation. The rate of ECMO use during the pandemic ranges from 0.5-1% of all hospitalized patients.

But ECMO therapy is not without risks, with nosocomial infections being one of the most frequent complications. These infections are described in up to 64% of patients undergoing this technique, with rates of 30.6 infectious episodes per thousand days of device use according to the ELSO prevalence study [1]. The factors that are directly related to the development of infection during ECMO therapy are adult age, the severity of the underlying disease, immunosuppression, the duration of ECMO support (from the second week of assistance, the chances of developing any infection exceed 50%), the ICU stay duration, as well as the support modality (in adults, veno-arterial therapy). The development of these infections is associated with increased mortality [2,3].

Primary bacteremias are the most frequently described infections during the extracorporeal therapy. But other infections associated with invasive devices, such as catheter-associated urinary tract infection and mechanical ventilation associated pneumonia (VAP) also have an increased incidence (the latter, in our environment, around 15 episodes per thousand mechanical ventilation days) [4].

However, diagnosing nosocomial infection in patients undergoing ECMO can be challenging. The blood exposure to the oxygenating membrane can provoke a systemic inflammatory response even in the absence of infection, a factor that in turn limits the validity of biomarkers such as procalcitonin and C-reactive protein for the infection diagnosis. The heat-cold exchanger used to regulate the body temperature interferes

with the detection of the febrile response to infection. In addition, it is the extracorporeal membrane itself that will ensure the oxygenation (and decarboxylation) of the blood, factor that can mask the impact of the infection on gas exchange in the lungs. All this can make the clinical diagnosis of VAP difficult, and also makes that some predictive scores of prognosis and evolution, such as the Clinical Pulmonary Infection Score (CPIS) [5], have a limited accuracy in this context.

In the case of our immunosuppressed patient, after having undergone conventional mechanical ventilation and ventilation in the prone position, she required connection to ECMO due to prolonged refractory hypoxemia, which prolonged her ICU stay, all of them factors that favored the appearance of several episodes of nosocomial infection, including VAP. In this case, the clinical and radiological diagnosis was microbiologically confirmed.

Despite specific antibacterial combinations, the patient developed a refractory septic shock caused of multidrug-resistant *P. aeruginosa*. The aggressiveness of the infection could be documented in the radiographic series and in the chest CT scan, which showed lung parenchyma cavitation, a factor that made it difficult to control the infection source.

Unfortunately, our case confirms the already published findings that patients with SEL who suffer from ARDS in the context of SARS-CoV-2 virus infection have a higher risk of mortality compared to patients without lupus disease. This risk is also higher than that of other morbidities such as arterial hypertension, diabetes mellitus, solid organ transplantation, smoking, alcoholism, obesity, solid neoplasms, and chronic heart, kidney, lung, or liver diseases, which all are also predisposing factors for increased mortality in the ARDS associated to SARS-CoV-2 infection [6].

CONFLICTS OF INTEREST

The authors declare no conflict of interest

REFERENCES

1. Bizzarro MJ, Conrad SA, Kaufman DA, *et al.* Extracorporeal Life Support Organization Task Force on Infections ECMO. Infections acquired during extracorporeal membrane oxygenation in neonates, children, and adults. Pediatr Crit Care Med 2011;12:277–81.
2. Babaro R, McLaren G, Boonstra P, et al. Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry. Lancet. 2020;396:1071-78
3. Montgomery VL, Strotman JM, Ross MP. Impact of multiple organ system dysfunction and nosocomial infections on survival of children treated with extracorporeal membrane oxygenation after heart surgery. Crit Care Med. 2000;28:526–31.
4. Informe ENVIN-COVID 2020. Grupo de trabajo de Enfermedades Infecciosas y Sepsis. Sociedad Española de Medicina Intensiva, Crítica y Unidades Coronarias. Disponible en: https://hws.vhebron.net/envin-helics/Help/COVID19/ENVIN-COVID_Informe_20_1.pdf
5. Luna CM, Blanzaco D, Niederman MS, et al. Resolution of ventilator-associated pneumonia: Prospective evaluation of the clinical pulmonary infection score as an early clinical predictor of outcome. Crit Care Med. 2003;31(3):676-82.
6. Bertoglio I, Miranda J, Daffre D, et al. Poor Prognosis of COVID-19 Acute Respiratory Distress Syndrome in Lupus Erythematosus: Nationwide Cross-Sectional Population Study Of 252 119 Patients. ACR Open Rheumatol. 2021; 3(11):804-11.